Preface.

The Japanese Cancer Research Society was founded on April 2, 1908, and ranks as one of medical societies in Japan allied to International Cancer Research Association. There is no doubt that the investigation of the important points on the nature and therapeutic treatment of tumors, which are essentially international in character can not be carried out, without any association to those investigating bodies in other countries. No nation acting alone can perform by any means the full researches on the oncological subjects.

Ever since the foundation of the Society we have endeavoured to contribute to the progress of cancer researches in various ways, and the chief works which we have done so far are briefly summarized as following:

1. Annual meeting of the Society held in connection with Japanese Pathological Society, in which the results of many research works on the oncological and allied subjects were reported.

2. The publication of the quarterly journal "GANN", which were sent to Cancer Research Societies and workers in other countries and to make an inter-change with medical journals published in other countries.

3. The scholarships which are awarded to worthy workers among the members of the Society and the prize-giving to those workers who carried out execellent and good research works were established for the sake of encouragement of the members.

4. A supplementary offering of money for the expense of patients suffering from malignant tumors who are admitted to hospitals and undergoing to the scientific investigation.

These works of the Society above described have been important contributions made to the science of medicine or oncology, and it is especially noteworthy that several important works have

been done under this scholarship. The total sum of money yielded to the enthusiastic workers and the number of them awarded this scholarship has been gradually increased, and this scholarship amounted to about ¥ 5,000 in 1922 and was awarded to sixteen men. Many of these contributions laid before the Society are the result of laborious research by those awarded workers. As an example may be mentioned " Experimental Study of the Pathogenesis of Carcinoma " by Prof. Dr. K. Yamagiwa (an honorary member of the Society) and Dr. K. Ichikawa, which has been recently accepted by many authors almost throughout the world and has been an important contribution to the determination of the nature and the histological developement of epithelial neoplasms.

Besides the above mentioned purposes, which shall be continued eagerly, the Society has an intention to establish a special cancer research institute and a hospital in connection with it, for the purpose of practical investigation on early diagnosis and therapeutic treatment of malignant neoplsms. To accomplish these intentions step by step, the Society recently finished the fitting up of a most advanced X-ray apparatus, which will be chiefly used for treatment. It is scarcely doubted that the successful accomplishment of the investigation on tumors can not only be fulfilled by the laborious investigations of medical men and scientific workers, but also by an allied assistance offered by all social classes all the world over. So we hope that our Society should be sufficiently supported by all classes for the successful performance of our essential purposes. There are a considerable portion of population auffering from the malignant tumors, and it is very necessary to establish quickly a completely arranged organization for the investigation and application of therapeutic treatments of malignant tumors, which are pronounced incurable.

On May, 25, 1922 H. I. H. Prince Fushimi Jun. became the President of Japanese Cancer Research Society, and it has exerted a great influence on the promotion of this society's purposes.

At this meeting the adresses were delivered by Dr. Honda, Dr. Nagayo, Dr. Yamagiwa and Dr. Dohi.

The Japanese Cancer Research Society is anxious to have publications, in which the results of research works on tumors are reported, and to introduce the results of those works by translation into Japanese as a part of the Society's work. We are now sending the journal "GANN" translated in foreign languages, in which the results of research works performed by the members in 1922 are abstracted and we should be very glad if an exchange between the publications reported in other countries and the "GANN" could be arranged, so that both of us may have the benefit of knowing the works which have been carried out in different parts of the world.

The number of members in the Society are now two hundreds and eighty.

February, 1923.

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Experimental Investigation on the Antibody-formation against the transplantable Mouse Carcinoma.

(I. Report).

By

Prof. Dr. **Katsusaburo Yamagiwa**
and
Dr. **Tetsuji Kimura.**

(*From the Pathological Laboratory of the Imperial University in Tokyo.*)

(With PLATE I.)

Methods.

The authors injected some tumor mass (1–5 gm.) intraperitoneally into a rabbit; this treatment was repeated several times, then the rabbit ("treated rabbit") was bled from veins of ears or the carotid and its serum was obtained ("anti-serum"). Also some internal organs (spleen, mesenteric lymph nodes and bone marrow) of a thus treated animal were finely dissected with scissors and slightly ground up, then shaken with addition of some sterile normal saline solution for one or two hours. This mixture was centrifuged in centrifuge tubes at moderate speed for twenty or thirty minutes and the supernatant fluid thus obtained was used as "anti-organ-extracts" in the experiment.

Next, the tumor tissue was very finely dissected with scissors and mixed with the above mentioned "anti-serum" or "anti-organ-extracts" in large centrifuge tubes, then plugged with rubber stoppers. As control, the authors used normal saline solution and the blood serum ("normal serum") or organ-extracts

(" normal organ-extracts ") of an untreated rabbit, which were obtained by the method above described.

These centrifuge tubes, which contain a mixture of the tumor mass with a normal saline solution or serum or organ-extracts of treated or untreated rabbits, were incubated at 37°C. for four or five hours, being several times gently shaken ; and then placed in the ice-chest for twelve or sixteen hours. Then add some salt solution to these mixtures and centrifuged. This process is repeated three times to insure thorough washing of the tumor mass to remove the traces of mixed serum or organ-extracts.

The tumor mass thus treated was implanted in the mice, which were grouped in three, four or five lots according to the number of mixtures used in the experiment.

Then observing the transplantability and the subsequent rate of growth of the tumor, the authors intended to see how the further growth of tumors *in vivo* was influenced by mixing with those serum or organ-extracts of treated and untreated rabbits *in vitro*.

The Effect of " Anti-serum " upon the Growth Energy of Tumor Cells.

First we carried out the preliminary experiments for five times repeatedly, using 60–90–120 mice for inoculation. Results of these experiments showed that there was nothing of retarding effects on tumor growth to be seen in " anti-serum " used by us. Furthermore we repeated accordingly four times the identical procedure in Experiment I., II., III., and IV., as to draw more clearer conclusion on the effect of " anti-serum " upon the tumor cells.

EXPERIMENT I.

Treated Rabbit, No. 7.

29/X,	1917.	Tumor mass.		3.0 gm.	injected	intraperitoneally.
2/XII,	,,	,,	,,	5.0 ,,	,,	,,
16/ ,,	,,	,,	,,	3.0 ,,	,,	,,
21/ ,,	,,	,,	,,	1.5 ,,	,,	,,
26/ ,,	,,	,,	,,	2.5 ,,	,,	,,
31/ ,,	,,	,,	,,	3.0 ,,	,,	,,
7/ I,	1918.	,,	,,	3.0 ,,	,,	,,
11/ ,,	,,	bled from the right carotid and thus obtained anti-serum was used in a preliminary experiment.				
27/VI,	,,	Tumor mass		3.0 gm.	injected.	
17/VII,	,,	,,	,,	6.5 ,,	,,	,,
24/ ,,	,,	,,	,,	3.0 ,,	,,	,,
27/VIII,	,,	,,	,,	5.0 ,,	,,	,,
2/IX,	,,	,,	,,	4.0 ,,	,,	,,
9/ ,,	,,	bled from the left carotid, and thus obtained serum was used for Exp. I.				

Group.	Mixture.				Mice inoculated.
A.	0.85% NaCl-solution	13 ccm.	Tumor-mass	1.5gm.	30
B.	Normal-serum	,,	,,	,,	,,
C.	Anti-serum	,,	,,	,,	,,
D.	Inactivated Anti-serum	12 ccm.	,,	,,	,,
	guinea-pig-serum 2 ccm. as complement.				

These mixtures were incubated at 37°C. for five hours and then inoculated.

Result:— As is shown in chart of Exp. I., we could not recognize any depression of growth energy of tumor cells inoculated in groups C and D, when compared with the sizes of tumors of animals in groups A and B on a given day.

EXPERIMENT II.

Treated Rabbit, No. 17.

29/XI,	1918.	Body-weight,	2440 gm.	Tumor-mass,	3.0 gm.	injected.
4/XII,	,,	,,	2680 ,,	,,	5.0 ,,	,,
12/ ,,	,,	,,	2470 ,,	,,	5.0 ,,	,,
22/ ,,	bled from the left carotid, the blood serum thus obtained was used for this experiment.					

Group.	Mixture.				Number of Mice inoculated.
A.	NaCl-solution,	12 ccm.	Tumor mass,	1.2 gm.	22

B.	Normal-serum,	12 ccm.	Tumor mass, 1.2 gm.	23
C.	Anti-serum,	,,	,, ,,	22

Shaken for one hour, incubated at 37°C. for 5 hours, laid in ice-chest for 13 hours, and then used for inoculations.

In this experiment, as is shown in chart of Exp. II., "anti-serum" showed no hindering effects upon the growth of the inoculated tumors by mixing.

EXPERIMENT III.

Treated Rabbit, No. 15.

15/XI,	1918,	Body-weight,	2080 gm.	Tumor-mass, 5.0 gm.	injected.
24/ ,,	,,	,,	2100 ,,	,, 3.0 ,,	,,
12/XII.,	,,	,,	1930 ,,	,, 3.0 ,,	,,

5/III., 1919, bled from the carotid to kill, and thus obtained anti-serum and anti-organ-extracts from the spleen and the mesenteric lymph-nodes were used for mixing with tumor-mass.

Group.	Mixed with		Tumor-mass.	Mice inoculated.
A.	Normal, NaCl-solution	15 ccm.	1.0 gm.	32
B.	Anti-spleen-extract	10 ,,	,,	,,
C.	Anti-lymphgl.-extract	15 ,,	,,	,,
D.	Anti-serum	20 ,,	,,	,,

Incubated at 37°C. for 6 hours, laid in ice-chest for 14 hours, and inoculated (to be discussed with the result of Exp. IV).

EXPERIMENT IV.

Treated Rabbit, No. 14.

14/XI,	1918.	Body-weight	2200 gm.	Tumor-mass	1.0 gm. injected.
19/ ,,	,,	,,	2450 ,,	,,	1.0 ,, ,,
24/ ,,	,,	,,	2515 ,,	,,	1.0 ,, ,,
4/XII,	,,	,,	2540 ,,	,,	1.0 ,, ,,
21/IV,	1919	,,		,,	3.0 ,, ,,
27/ ,,	,,	,,	2670 ,,	,,	3.0 ,, ,,

8/V, ,, ,, 2700 ,, Bled from carotid to kill, and anti-serum, anti-organ-extract from the spleen and mesenteric lymph-nodes were obtained for this experiment.

Group.	Mixed with	Tumor mass.	Mice inoculated.
A.	NaCl-solution	15 ccm.	1.0 gm.	40
B.	Anti-spleen-extract	,,	,,	34

C. Anti-lymphgl.-extract	15 ccm.	1.0 gm.	37
D. Anti-serum	20 „	„	34

Incubated at 37°C. for 6 hours, laid in ice-chest for 12 hours, and then used for inoculation.

Results of Exp. III. and IV.:— As is shown in chart of these experiments, they showed the identical results with those observed in Exp. I. and II., no marked difference between the growth energy of the tumor in groups mixed with "anti-serum" and of lots mixed with NaCl-solution or "normal-serum" being recognized.

So the outcome of these four experiments was identical with that observed in the preliminary experiments and not the slightest indication of retarding action on tumor growth could be discovered in any of the experiments.

On the depressing Effect of "Anti-Organ-Extracts" upon the Growth Energy of Tumors.

Failing to prove any indication of hindering action on tumor growth in "anti-serum", the following experiments were undertaken to determine whether the above mentioned "organ-extracts" of treated rabbits show any growth retarding effect on tumor cells by mixing *in vitro*. It will also be noted in the chart of the preceding experiments III. and IV. that the growth energy of the tumors in groups of "anti-spleen-extract" and "anti-lymphgland-extract" shows somewhat distinct depression, the size and the percentage of susceptibility of the grafted tumors to be smaller than those of the NaCl- and Anti-serum lots being observed.

Furthermore we carried out repeatedly the following three experiments to study more certainly the influence of those "anti-organ-extracts" upon the growth energy of tumors, comparing with those of "normal organ-extracts" of untreated rabbits used as controls.

EXPERIMENT V.

In this experiment 172 mice were used for inoculation; but having examined the growth of the transplanted tumors on a given day, it was found that only in

a few mice of some lots were the positive transplantability to be seen and in other groups entirely negative results. In such a case, it is difficult to draw any clear conclusion from the experimental result, so we have to omit this experiment out of the consideration to determine the retarding effect of those "organ-extracts".

EXPERIMENT VI.

Treated Rabbit, No. 22.

8/VII,	1919.	Body-weight		Tumor mass,	2.0 gm.	injected.
16/ „	„	„	2410 gm.	„	2.5 „	„
7/VIII,	„	„	2530 „	„	2.5 „	„
16/ „	„	„	2435 „	„	2.5 „	„
7/XII,	„	„	2785 „	„	2.5 „	„
12/ „	„	„	2595 „	„	2.5 „	„
22/ „	„	killed with an occipital blow, and "anti-organ-extracts" of the spleen, mesenteric lymph nodes and bone marrow were obtained, being mixed with tumor mass in this experiment.				

Group.	Mixed with,		Tumor mass.	Number of mice inoculated.
A.	NaCl-solution.	15 ccm.	0.8 gm.	15
B.	Anti-spleen-extr.	10 „	„	„
C.	Anti-lymphgl.-extr.	15 „	„	„
D.	Anti-bone-marrow-extr.	10 „	„	„
E.	Normal-spleen-extr.	10 „	„	„
F.	Normal-lymphgl.-extr.	10 „	„	„

Incubated at 37°C. for 4 hours, laid in ice-chest for 16 hours, and inoculated.

As is shown in chart, the susceptibility and the growth energy of transplanted tumors showed relatively better results in groups A. D. E. than in grpups F. B. C., though very marked differences between them could not be observed.

EXPERIMENT VII.

Treated Rabbit, No. 28.

15/VII.	1919.	Body-weight	1675 gm.,	Tumor mass,	1.5 gm.	injected.
7/VIII,	„	„	2070 „	„	2.0 „	„
7/XII,	„	„	2415 „	„	2.5 „	„
12/ „	„	„	2440 „	„	1.5 „	„
12/II,	1920.	„	2600 „	„	3.0 „	„
17/ „	„	„	2350 „	„	2.0 „	„
23/ „	„	„	2520 „	„	4.0 „	„

3/III, „ Killed with an occipital blow, and "anti-organ-extracts" of the spleen and mesenteric lymph nodes were obtained for this experiment.

Group.	Mixed with,		Tumor mass.	Number of mice inoculated.
A.	NaCl-solution	15 ccm.	1.5 gm.	18
B.	Anti-spleen-extract	10 „	„	„
C.	Anti-lymphgl.-extr.	15 „	„	„
D.	Normal-spleen-extr.	10 „	„	„
E.	Normal-lymphgl.-extr.	15 „	„	„

Incubated at 37°C. for 5½ hours, laid in ice-chest for 14 hours, and then used for inoculation.

The results of this experiment, as is shown in chart, indicate that by mixing with tumor mass *in vitro* "anti-organ-extracts" of treated animals show somewhat marked depressing action upon the growth energy, in comparison with the effect of "normal-organ-extracts" of untreated animals.

As is shown in chart of Exp. III. IV. VI. and VII., there is more or less markedly recognized the diminishing susceptibility and the depressive action upon the growth energy of transplanted tumors in lots of "anti-organ-extracts" by the above mentioned procedure, being compared with those in lots of "normal-organ-extracts."

Anatomical Features of the Treated and Untreated Animals used in the Experiments.

Macro- and microscopical examinations showed that there were some marked differences between the features of the spleen and mesenteric lymph nodes of treated and untreated rabbits. To avoid much confusions, we briefly summarized up those chief descriptions in discussion in the following tables:—

TABLE I. **Showing the Weights of the Spleen and the Mesenteric Lymph Nades of Treated and Untreated (or Normal) Rabbits.**

No. of Animals.	Repeated Times of Injection.	Total Amount of Tumor Mass injected.	Intervals between Death & last Injection.	Body-weight.	Weight of Spleen.	Weight of Mesenteric Lymphglands.
Treated Rabbits:						
14.	6	10.0 gms.	12 days.	2700 gm.	2.0 gm.	3.5 gm.
15.	3	11.0 „	ca. 3 mos.		1.0 „	3.0 „
19.	4	10.0 „	11 days.	2175 „	1.8 „	3.5 „
22.	6	14.5 „	10 „	2555 „	1.8 „	3.5 „
28.	7	16.5 „	9 „	2295 „	1.2 „	4.2 „
29.	3	8.0 „	9 „	2310 „	1.3 „	2.9 „
Untreated or Normal Rabbits:						
In Exp. V.				2000 „	2.0 „	3.0 „
In Exp. VI.				2140 „	1.4 „	2.0 „
In Exp. VII.				3605 „	1.0 „	2.0 „
(In Exp. VIII.)				1955 „	1.0 „	5.7 „

TABLE II. **Showing the Histological Features of the Spleen of Treated and Untreated Animals.**

No. of Animals.	Lymphfollicles.		Germ-Centers.		
	Numbers.	Sizes.	Distinctness.	Sizes.	Mitotic Figures.
Untreated Rabbits:					
Exp. V.	numerous	small	almost invisible		
Exp. VI.	numerous	large or small	moderately	large or small	a few number.
Exp. VII.	numerous	small or normal	distinct	small	a few number.
Exp. VIII.	a few	small or normal	indistinct in a large number	small	a few number.

Treated Rabbits:					
No. 14.	numerous	various	distinct	large	numerous
„ 15.	numerous	normal	distinct	large	not so numerous
„ 19.	numerous	normal	distinct	large	numerous
„ 22.	numerous	normal	distinct	large	numerous
„ 28.	normal	various	moderately distinct	small	a few number
„ 29.	numerous	normal or large	distinct	large	numerous

TABLE III. **Showing the Histological Features of the Mesenteric Lymph Nodes of Treated and Untreated Animals.**

No. of Animals.	Cortical Lymphnodules		Germ-Centers			Comparison between Widths of Cortial & Medullary Portions.
	Size.	Margined.	Distinctness.	Size.	Mitotic figures.	
Untreated or Normal Rabbits:						
Exp. V.	small	sharply	distinct in a large number	small	numerous	C < M
Exp. VI.	somewhat enlarged	indistinctly	almost indistinct	„	a few	C < M
Exp. VII.	small	sharply	„	„	„	C < M
Exp. VIII.	„	„	„	small or moderate	„	C = M
Treated Rabbits:						
14.	large	indistinctly	distinct	large	numerous	C > M
15.	various	„	„	small	a few	C > M
19.	large	„	„	large	numerous	C > M
22.	„	„	„	„	a few	C > M
28.	„	partially indistinct	„	moderate	moderate	C > M
29.	„	indistinctly	moderately	„	„	C > M

From the above mentioned tables, it is found that the spleen and mesenteric lymph nodes of treated rabbits were slightly enlarged in comparison with those of untreated rabbits; but this difference between them proved not striking.

As regards to the histological features of the spleen and mesenteric lymph nodes, it should be noted that the two groups of treated and untreated animals differed decidedly in the general tendency of increased or decreased activity in lymphoid tissues.

The general histological appearance of the spleen of treated rabbits showed an enlargement of the Malpighian bodies, especially of germ centers, and the superabundance of mitotic figures in them, while in the spleen of untreated rabbits the germ centers of Malpighian bodies were small or indistinct and a few mitotic figures could be seen.

The changes in the mesenteric lymph nodes of the two groups were also entirely parallel to those found in the spleen. In lymph nodes of treated animals were observed an enlargement of lymph follicles in cortex, germ centers and pulp cords, and numerous mitotic figures in germ centers. Compared to the features of lymph nodes in treated animals, the lymphoid tissus of lymph nodes in untreated animals showed a condition of hypoactivity in tissue proliferation (diminished in size of follicles and germ centers, and in number of mitotic figures).

Therefore the point to be emphasized in the microscopical study was the difference between the histological features of the lymphoid tissues in treated and untreated animals. In treated rabbits there were more or less marked indications of lymphoid hyperplasia, while a depleted condition of the lymphoid organs was to be observed in untreated rabbits.

Conclusions.

1. "Anti-serum" has no retarding effect upon the growth of the tumor cells *in vivo*.

2. "Anti-spleen-extract" of treated animals shows a more or less marked hindering effect on its growth.

3. "Anti-lymphgland-extract" of treated animals has also the same retarding effect on the growth of tumors as "anti-spleen-extract", but is a little weaker than that of the latter.

4. "Normal spleen-extract" shows no influence on the rate of the growth of tumors in comparison to that of the normal salt solution series; it is strikingly less significant than that of "anti-spleen-extract"

5. The effect of "normal lymphgland-extract" of untreated animals is inconstant, showing in some cases a marked retarding effect on the tumor growth and in others no preventing influences can be seen, so that no decisive conclusion can be drawn.

6. In treated rabbits there are observed more or less marked indications of increased lympho-activity, while in untreated a depleted condition of the lymphoid organs is to be seen.

A Case of Fibroplastic Myxoma in a Gold-Fish.

By

Dr. **Heinosuke Wago.**

(*From the Pathological Laboratory of the Institute for Infectious Diseases, Tokyo.*)

The author described on multiple tumors in a gold-fish, which lived in a pond in the garden of Mikawaya-Hotel at Hakone, Kanagawa Ken. Macroscopical examination showed multiple tumors of various sizes (miliary-"adzuki"-bean), and of pale reddish gray-white colour, which were scattered throughout on the whole body-surface (head, thorax, caudal fin, dorsal and pectoral fins, and

eyes). The tumors were generally spheroidal or polypoid in shape, and sharply margined, emerging from surroundings. The surface of tumors was smooth, being not covered with scales, and elastic firm in consistency. On cut-surface they appeared reddish gray-white and semewhat translucent.

Histological characters of these tumors were found to be almost identical. The tumor tissue was composed of abundant but delicate young fibrous tissue and fusiform fibroblasts mingled with a few spindle- or irregular-shaped cells, which possess the long branching processes. These fibroblasts and fusiform branching cells were loosely arranged and widely separated from one another, having formed a delicate meshwork of fine intercellular fibers, the spaces of which were filled with mucin-like substances. Round cell infiltrations or any other inflammatory indications were not to be observed.

According to the above described morphological characters, the author considered this tumor to be classified in Fibroplastic Myxoma. Having recognized no parasites or micro-organisms in the tumor tissue and internal organs, the author noted that it is impossible to decide any clear etiological factor in this case.

(*T. K.*)

On the Spindle-Celled Sarcoma in a Salmon.

By

Dr. **Yoshiaki Kazama.**

(*From the Pathological Laboratory of the Medical College, Niigata.*)

Among one thousand salmons (Oncorhynchus Keta), the author found a tumor in one of them. This fish, aged almost 5 years, was ca. 85 cm. in length and 6 Kilo. in weight. It appeared

externally in normal and there was nothing of important changes in internal organs to be seen. The tumor sited on the internal surface of the abdominal wall corresponded to the attached portion of the right pelvic fin, emerging into the peritoneal cavity showing an appended hemispherical shape. It was $6.5 \times 6.0 \times 3.0$ cm. in size, and generally elastic in consistency, being covered with fibrous capsule, which showed an engorgement of blood vessels and passed on gradually to the normal surrounding peritoneal surface. On cutting, it was observed that the tumor was of pale reddish gray-white colour and composed thoroughly of fibrous tissues, appearing soft and bloody in it's peripheral portion and centrally necrotic in places.

Histologically the tumor parenchym was mostly composed of fusiform cells, being cut up into islets of various sizes by stromatous fibrous tissue. Parenchym cells showed a considerable variation in the shape; so in the peripheral portion of the tumor directly below the fibrous capsule they showed fairly a fusiform shape of protoplasma with a spindle-shaped nucleus, while the tumor cells in central portion were polymorphic mixed with a few scattered giant cells. Karyomitotic figures were nowhere to be seen. The tumor tissue was not sharply margined and showed a destructive growth, infiltrating into the surrounding muscle fibers.

An intimate relationship between the tumor cells and stromatous fibrous tissue was recognized and the presence of intercelluiar fibrillar substances among the individual tumor cells observed. No marked round cell infiltration in the stromatous tissue to be found.

(*T. K.*)

Experimental Studies on the Tumor-Formation in the Internal Organs.

(I. Report.)

By

Dr. **Yoshiaki Kazama.**

(*From the Pathological Laboratory of the Medical College, Niigata.*)

(With PLATE II.)

It is quite well known that prolonged injury or irritation is a frequent forerunner of cancer and is acknowledged to have an important etiological significance. Recently several successful descriptions of attempts to produce the malignant new-growth experimentally by the application of various irritants have been reported by Fiebiger (Spiroptera neoplastica in rats), Yamagiwa and Ichikawa (Coal-tar painting in rabbits), Kopsch (Larves of Nematodes in frogs), and Bullock and Curtis (Cysticercus fasciolaris in rats), etc. Being stimulated by those reports and also by the anatomically and experimentally observed changes of an intestinal cancer due to the presence of Schistosomum japonicum, the author intended experimentally to produce the new-growth in the internal organs of the laboratory animals by application of various kinds of irritations. These experiments were exhaustively performed, having used many animals and several irritants variously applied, and the author described in details the anatomical changes of the organs irritated with many tables and illustrating plates.

The procedure performed and the results obtained in these experiments, might briefly summarized up as followings:

Animals used in experiments: Rabbit, Guinea-pig, rat, dog, fowl and pigeon.

Internal organs applied with irritations: Stomach, bladder, gall-bladder, intestinal canal and uterus.

Applied irritants: Irritations used in experiments are subdivided into: — (A). Mechanical irritants; diets, stone-particles, threads, fragments of mucous membrane. (B). Chemical irritants; Pityrol-injection, Pityrol-feeding, Lanoline-injection, Coal-tar-injection. (C). Chemicomechanical irritants; Pityrol-paraffine-pills, stone-particles-placing followed by Pityrol-placing.

Methods of application: These irritative substances were used mixed in diets to feed the animals, or injected with needles into the above mentioned organs. In a case of application with solid mass, as pills or particles, as irritants into internal organs, an incision is made through the wall of organs by surgical operation, and pills or particles are placed into through the opening, then the tissues were approximated edge to edge by sutures throughout. Thus irritations on the tissue are applied repeatedly or continuously for some durations.

Results: In the stomach and bladder of rabbits and in the stomach and gall-bladder of guinea-pigs, these irritant-applications resulted in producing not only an atypical proliferation of epithelium, but tumor-like new-growth or malignant tumors.

By application of chemical irritants (once or several times repeated injections with Pityrol or lanoline), there was found the urinary- or gall-stone formation in the bladder or gall-bladder simultaneously associated with formation of tumors.

As regards to the site of formation of the atypical epithelial proliferation or the new-growths, these pathological tissue proliferations were recognized at those portions, which are most frequently and intensively irritated and injured, *i.e.* margins of the ulceration of the stomach wall due to incision, injected portion with needles, or pyloric region where it is mechanically irritated by passage of diets. In majority the new-growth developes circumscribed and singly, while multiple developement is occasionally found.

Tumors produced in rabbits are papillary or nodular and mostly hemispherical in shape, and of pea or sparrow's egg size.

Those in guinea-pigs are also papillary- or nodular-shaped and hemispherically elevated from surroundings, and of "adzuki" or corn size. They are firm in consistency and coloured grayish white, showing often various-sized glandular lumens on cut-surface and being surrounded by thickened mucous membrane. Tumors of the stomach or bladder in rabbits show occasionally a central ulceration.

On the merely thickened mucous membrane, there are histologically found the hypertrophy and prolongation of epithelia associated with hyperplasia of submucous tissue, in which round cell infiltration and overfilling or new formation of blood-vessels are to be seen. In papillary- or nodular-shaped new-growths, there are dilatation, convolution and branching of glandular tissues and round cell infiltration throughout the whole walls — submucosa, muscularis and subserosa — to be recognized. The proliferated epithelium and glandular portion shows much irregularity, being observed a heterotopic invasion in submucosa and atypical infiltrating proliferation in muscularis or submucosa. The arrangement and normal relationship between epithelium and interstitial connective tissue became more and more irregular and atypical in morphological characters, and there is also more accerelated condition of karyokinetic process in cells. So the initially observed pathological process of atypical epithelial proliferation passes on gradually to the features of innocent papilloma or adenoma, leading at last to the formation of adenocarcinoma which is much malignant in morphological and biological characters.

Out of 18 cases of artificially produced adenocarcinoma of the gall-bladder in guinea-pigs, there are 6 cases of metastasis-formation to be confirmed; 4 of them in the liver and 2 in the abdominal and pectoral walls.

Experimental grafting into other animals with some adeno-carcinomata thus developed was attempted without any successful result.

There are marked differences among the possibilities to produce a successful developement of those pathological tissue proliferations experimentally, according to the species of animals used. In guinea-pigs and rabbits, irritations produce more easily the developement of atypical epithelial proliferation or new-growths, while in fowls, pigeons, rats and dogs the marked morphological change is rarely recognized by application with irritants in the similar way.

Difficulty to produce those pathological tissue proliferations by means of irritants-application differs also largely in individuals even when the same species of animals is used; some of them show a marked tissue proliferation shortly after the first application with irritants, while the other remain unchanged in spite of more prolonged and intensive irritation.

Furthermore there are observed distinct differences among the irritability of those internal organs in the same individual against the irritation, even when the similar irritant is applied. So in rabbits, the bladder is apt more easily to develope the morphological change by Pityrol-injection, while the stomach only slightly reacts against the similar procedure; in guinea-pigs the gall-bladder shows a significance of more increased irritability than the stomach and bladder.

From those above described results experimentally obtained, the author may infer: (1) That the successful developement of polyp, papilloma, adenoma and adenocarcinoma caused by the application of chemico-mechanical irritations is almost due to the identical pathologic process, which are observed in cases already reported by various workers (Fibiger, Kopsch, Yamagiwa and Ichikawa, Kon, Ueda, Honda, Ikematsu etc.). (2) That there are some different predisposing factors as regards to the developement of new-growths to be recognized, according to the difference of species of animals, of individuals and of the organs; so it is to be remembered that the developement of tumors takes place

only when the necessary and sufficient conditions would be fulfilled with the total sum of character and intensity of irritations and of predisposing factors in organs, individuals and species of animals. (3) That the experimental observation, in which the developement of tumors is produced by placing of stone-particles or in association with gall-stone formation, is in coincidence to the fact, in which the frequent ocurrence of the gall-bladder cancer combined with prolonged presence of the gall-stones is recognized clinically and anatomically

(*T. K.*)

Description of Plate II.

Formation of malignant adenoma due to a placing of stone-particle into the gall-bladder of the guinea-pig (*Fig. 1–3*).

Fig. 1. Section of the tumor (Low power microphotograph).
A.D. Destructive adenoma, L. Liver, GB. Thickened walls of the gall-bladder.

Fig. 2. Section of the tumor (High power microphotograph).
D. Atypically proliferated glandular tubules, I. Stromatous tissue.

Fig. 3. Section of the Metastatized tumor in the thoracic wall (Low power microphotograph).
M. Metastatized tumor tissue. B. Thoracic wall, K. Rib cartilage.

Formation of malignant adenoma due to the lanoline injection into the gall-bladder of the guinea pig. (*Fig. 4–5*).

Fig. 4. Section of the tumor. (Low power microphotograph).
AD. Destructive adenoma, GB. Normally appeared wall of the gall-bladder, L. Liver.

Fig. 5. Section of metastatized tumor in the abdominal wall (High power microphotograph).
M. Metastatized adenoma tissue, OS. Osteoid tissue, BW. Abdominal wall, BM. Transverse section of abdominal muscles. P. Peritoneum.

The Effects of Chloroform Narcosis upon the Growth of the transplanted Animal Tumors.

By

Dr. **Tetsuji Kimura,** Dr. **Katsutoshi Ohba**
and
Dr. **Yoshiji Wada.**

(from the Pathological Laboratory of the Tokyo Jikeikai Medical University in Tokyo.)

The authors referred to experiments reported by *Gaylord and Simpson* in which it was shown that by bleeding and narcosis (chloroform and ether) a rapid growth of transplanted mouse carcinoma could be induced. The effect of bleeding was also apparently confirmed by careful studies of *Tadenuma and Okonogi* with chicken sarcoma and mouse carcinoma, in which they showed that the removal of primary tumors combined with hemorrhage caused metastasis more frequently and those metastatic nodules to grow to a larger size than was the case in control animals where the primary tumors were not touched. Furthermore the authors referred to the experiment described by *Much* in which it was shown that by injections of lactic acid non-pathogenic microorganisms could become virulent to animals. In connection with this experiment by *Much, Rostock* reported that by treating in similar way the percentage of transplantability of a mouse tumor and rapidity of it's growth could be increased.

For the purpose of testing again the question on the effect of anesthesia and injection of lactic acid upon the growth of transplanted animal tumors, experiments were planned with Flexner rat carcinoma (F. R. C.), Jensen rat sarcoma (J. R. S.) and Kato rabbit sarcoma (K. K. S.). The rats used in the experiments were compared as to size and age. They were divided into two or three lots of seven or fourteen respectively, and were inoculated

with a mass of small fragments of tumor finely dissected with scissors by special syringe method. Immediately or a few days after inoculation the animals in one of the lots were anesthetized with chloroform, which was done by placing them individually in a glass jar and enough chloroform being dropped to cause them to fall over. This short anesthesia was nine or thirty times repeated each day or every two days, and being measured and chartered the size of tumors and the weight of animals at intervals of seven or fourteen days, effects of narcosis were examined. The experiment with rabbit sarcoma was carried out in similar way, being anesthetized almost each day for one month long.

Series of experiments, which the authors carried on, were as followings:

	Number of animals.		Frequency of
Strain of tumors.	Controls.	Anesthetized.	Anesthesia.
J. R. S. Exp. I.	13	14	13 times
„ „ III.	7	7	17 „
F. R C. Exp. I.	10	13	21 „
„ „ III.	12	12	9 „
K. K. S. Exp. I.	4 (8 tumors)	4 (8 tumors)	30 „

From results of these experiments it was shown that there would be recognized no distinct effects upon transplantabilities and growth of inoculated tumors caused by anesthesia.

To test the effect of surgical operation combined with anesthesia, the rats were inoculated with Flexner rat carcinoma on both sides of the back (F. R. C. Exp. II.), comparing the size of growing tumors after inoculation, the animals were divided into two lots of twelve (controls) and thirteen (operated), in the latter of which one of inoculated tumors war individually removed by surgical operation under chloroform narcosis. Then examining the rapidity of the growth of the remaining tumors in operated

animals (bearing one tumor) in comparison with those of untreated control ones (bearing two tumors), the authors intended to observe the effect of this surgical treatment and of removal of a tumor on one side upon the growth of the remained tumor in animal bodies. Of the remained tumor in treated animals, none showed a marked increase in size as compared with the tumors of the control animals. Most of the treated animals lived longer than those in the control lot, which had two tumors.

Furthermore to test the effect of the lactic acid injection (0.5% solution) upon the growth of tumors, the authors injected subcutaneously 1–2 ccm. of the solution one or three times after a tumor inoculation as followings:

	Number of animals.		Frequency of
Strain of tumors.	Injected	Controls	injection (amount.)
J. R. S. Exp. III.	7	7	once (2 ccm.)
F. R. C. Exp. III.	12	12	three times (4 ccm.)

Moreover among animals used in F. R. C. Exp. II. there were seven rats which showed very slow growth of the tumor, and they were put on lactic injection (2 ccm.) in similar way. In these experimental investigations, the difference between the sizes of tumors in the treated and the control animals was so small that no conclusion can be drawn either way; and also any increased transplantability of tumors could not be recognized in treated animals, when comparison is made between the treated and the control rats. In F. R. C. Exp. III., being compared with the control animals, the treated showed rather retarded growth of inoculated tumors.

Their investigations lead to the following conclusions:

1. No marked effects to stimulate the growth of inoculated tumors were recognized in animals, which were repeatedly anesthetized or surgically operated under anesthesia, being compared with those of the control animals.

2. Of the lactic acid injection, there were no cases to be

observed, in which the transplantability and the growth of inoculated tumors was accerelated under treatment. (*Authors' abstract.*)

Beiträge zur Kenntnis der Sarkomentwicklung bei der Transplantation von Mäusekrebs.

Von

Tameyoshi Asada.

(*Aus dem pathologisch-anatomischen Institut der Kaiserl. Universität zu Fukuoka, Japan. Leiter: Prof. Dr. Tawara*).

(Mit TAFEL III.)

Diese Erscheinung hat *L. Löeb* zuerst im Jahre 1903 bei seiner Transplantation an Mäusekrebs beobachtet. Er fand, daß schon in der zweiten Impfgeneration aus dem ursprünglichen Adenokarzinom das Spindelzellen-, Fibrosarkom oder die gemischte Form von Sarkom und Karzinom, in der dritten Impfgeneration hauptsächlich das reine Sarkom entstanden. Die weitere Transplantation war wegen des Mangels an japanischen Mäusen misslungen. Über die Erklärung dieser Sarkomentwicklung bei der Transplantation von Mäusekrebs sind bisher drei Möglichkeiten in Betracht gekommen, erstens, daß der ursprüngliche Tumor mit Keimen der bei den Geschwülste ausgestattet sei, zweitens, die Umwandlung von Karzinomzellen in Sarkomzellen, drittens, daß aus dem interstitiellen Bindegewebe des Karzinoms durch Reizung das Sarkom entstehte. Dabei meinte *L. Loeb* daß bei dieser allmählichen Sarkomentwicklung aus Mäusekrebs die Parasiten im Spiele wären, die auf das Bindegewebe einen Reiz ausüben. *Ehrlich* u. *Apolant* fanden 1905 bei der Transplantation von Adenocarcinom in der 14. Impfgeneration ein reines Spindelzellensarkom entstehen, das bis zur 26. Impfgeneration mit immer gesteigerter Impfausbeute sich transplantieren liess. Diesen Befund erklärten

sie durch die Annahme, daß bei den fortgesetzten Transplantationen neben den Krebszellen auch Bindegewebe verpflanzt wird, das durch die zahlreichen Tierpassagen im fremden Organismus eine bis zur Geschwulstbildung sich steigernde Proliferationsfähigkeit erhält. Dagegen äussert sich *Schlangenhaufer* dahin, daß der Ausgangstumor den Sarkomkeim d. h. eine indifferente embryonale Zellform enthalte, die sich durch Reizung zur Geschwulst entwickeln könne.

Krompecher nimmt an auf dem Grund von embryologischen und zoologischen Tatsachen, dass sich die epithelialen Zellen im biologischen Sinne bindegewebig umwandeln können, daß diese Umwandlung auch im pathologischen Tumorgewebe möglich sei.

Ich beobachtete auch diese Erscheinung bei der Transplantation von einem zufällig in unserem Institute entdeckten Mäusekrebs sporadisch in fast allen Impfgenerationen, von der 2. bis zur jetzigen 15. Generation: ich konnte nämlich unter meinen 180 Impftumoren histologisch nicht nur 24 Fälle von Geschwülsten nachweisen, welche neben eigentlichem Karzinomgewebe in verschiedenem Masse auch spindelzellensarkomatösen Bestandteil enthielten, sondern auch weitere 8 Fälle von rein sarkomatösem Bilde entdecken, von welch letzteren sogar ein Fall von der 12. Impfgeneration bis jetzt als solcher wiederholt sich gut transplantieren liess.

Was den Entstehungsmodus des sarkomartigen Gewebes innerhalb des implantierten Mäusekrebses anbelangt, so konnte ich bei genaueren morphologischen und biologischen Untersuchungen keineswegs die obengenannten Hypothesen bestätigen; vielmehr möchte ich glauben, daß das neu entstandene Sarkombild nur ein scheinbares und nichts anders als Krebs selbst ist, indem dieser nur morphologisch das sakromatöse Aussehen darbietet. Diese Erwägung stützt sich auf folgende Tatsachen.

Impfresultat und Wachstumsenergie der neu entstandenen Sarkome.

Unser Mäusekrebs hat durchschnittlich 60%ige Impfausbeute. Wenn einmal sarkomatöse Bestandteile innerhalb des Krebsgewebes entstehen, zumal die vollkommene sarkomatöse Umwandlung geschieht, so sehen wir immer deutliche Herabsetzung der Impfausbeute und gleichzeitig der Wachstumsenergie.

Generation	Fall	Tiernummer	Histolog. Befunde	Impfprozent
VI	1	No. 16. (10)	Carc. u. Sarc.	43%
	2	23/VI Tr.	rein Sarc.	—
	3	I/VII Tr.	Carc. u. Sarc.	57%
	4	II/VII Tr.	Carc. u. Sarc.	0%
VII	5	Nr. 1 (1)	rein Sarc.	—
	6	Nr. 1 (3)	rein Sarc.	—
	7	K. 11 (4)	Carc. u. Sarc.	5%
	8	Nr. 5 (1)	rein Sarc.	2%
	9	Nr. 5 (3)	rein Sarc.	0%
	10	Nr. 5 (4)	rein Sarc.	6%
	11	Nr. 16 (10)	Carc. u. Sarc.	5%
VIII	12	Nr. 25 (4)	rein Sarc.	3%
	13	K. 15 (4)	Carc. u. Sarc.	62%
IX	14	Nr. 45 (2)	Carc. u. Sarc.	20%
	15	Nr. 45 (3)	Carc. u. Sarc.	14%
	16	K. 24 A. I.	Carc. u. Sarc.	—
X	17	Nr. 50. B. 3.	Carc. u. Sarc.	—
	18	Nr. 59 (7)	Carc. u. Sarc.	60%
	19	Nr. 88 (2)	Carc. u. Sarc.	57%
	20	Nr. 96 (7)	Carc. u. Sarc.	—
XI	21	Nr. 94 (1)	Carc. u. Sarc.	—
	22	Nr. 94 (6)	Carc. u. Sarc.	—
	23	Nr. 94 (7)	rein Sarc.	14%!
	24	K. 26. A. 2.	Carc. u. Sarc.	—
	25	K. 30. B. 4.	Carc. u. Sarc.	—
	26	K. 30. B. 2.	Carc. u. Sarc.	—
XII	27	Nr. 54 (7)	Carc. u. Sarc.	—
	28	K. 32 (7)	Carc. u. Sarc.	—
XIII	29	G. 8 (3)	Carc. u. Sarc.	91%
XIV	30	Nr. 67 (3)	Carc. u. Sarc.	—
	31	Nr. 74 (3)	Carc. u. Sarc.	—
XV	32	Ov. XII (1)	Carc. u. Sarc.	50%

Wie wir aus der Tafel ersehen können, sinkt die Impfausbeute der gemischten Form von Sarkom und Karzinom durchschnittlich bis 38%, viel deutlicher bei der rein sarkomatösen Form, so dass von den letzteren 8 Fällen nur ein einziger Fall sich bis zu mehreren Generationen transplantieren liess. Selbst in diesem Falle (Nr. 94. 7.) war die Virulenz so schwach, daß mit der gewöhnlichen Stückimpfung kaum weiter transplantiert werden konnte. Hier fand ich eine neue Impfmethode, die Impfung von hochvirulenten Keimen, die durch absichtliche Rezidivierung des Muttertumors gewonnen wurden. Alle diese Eigenschaften weichen von denjenigen der gewöhnlichen transplantablen Sarcome ab, welche eine höhere Impfausbeute und Wachstumsenergie als Krebs zu zeigen pflegen.

Histologische Untersuchungen.

Die morphologischen Veränderungen der Geschwulstzellen, besonders der transplantablen Tumorzellen sind schon von vielen Autoren beobachtet. *T. Kato* sah bei dem transplantablen Chondrosarkom eines Haushuhnes spindelzellensarkom-und myxosarkomartige Veränderungen derselben Tumorzellen. *Fibiger* fand die sarkomatöse Umwandlung seines künstlich erzeugten Krebses in der dritten Impfgeneration.

Die primäre Geschwulst unseres Falles stellte ein fast typisches Bild von Adenocarcinom dar; schon in der zweiten Generation geht in den meisten Fällen der adenomatöse Bau verloren und zeigt hauptsächlich das Bild von Carcinoma solidum alveolare, ausserdem ist manchmal die Funktion von Alveolenbildung verloren und erscheint ein Rundzellensarcom, wenn die Tumorzellen einer ungünstigen Bedingung ausgesetzt sind. Viel häufiger verändern die eigentlichen Krebszellen ihre Form sicher langspindelförmig wie die Sarkomzellen, besonders in der Gegend von nekrotischen Herden.

Kurz gesagt, die Krebszellen unseres Falles verändern unter den Umständen leicht ihre Form spindelförmig.

Wenn wir die Sarkomentwicklung bei der Transplantation von Mäusekrebs genau betrachten, so finden wir, daß in den beginnenden Stadien immer zuerst die gemischte Form von Carcinom und Sarcom erscheint. Bis wir reine Spindelzellensarkome gewinnen, müssen wir in den meisten Fällen dieses Vorstadium längere Zeit verlaufen lassen. Wird dieses Sarcom im beginnenden Stadium mit dem mehrmals transplantierten reinen Sarcom verglichen, so findet man auffallende Unterschiede zwischen beiden: das im transplantierten Karzinomgewebe neu entstandene Sarcom besteht meist aus relativ kurzspindeligen, gewöhnlich noch kein Bündel bildenden Zellen, die während des weiteren Wachstumes oder bei wiederholten Transplantationen langspindelige Form annehmen und zugleich von einer fibrillären Grundsubstanz durchsetzt sind. Indem solche spindeligen Zellen mit beigemengten Bindegewebsfibrillen deutliche Zellbündel bilden, nach verschiedenen Richtungen gewunden verlaufen und sich untereinander verflechten, entsteht erst das Sarkombild, das von dem gewöhnlichen primären Spindelzellensarkom in nichts abzuweichen scheint. Das Bild ist aber nur ein scheinbares: denn es dürfte keine allmähliche Umgestaltung von kurzspindeligen Zellen zu lang spindeligen, sondern müsste von Anfang an ein ziemlich endgültiges Bild von Spindelzellensarkom darbieten, wenn das Sarkom wirklich bindegewebiger Natur wäre. (Vergleich PLATE III. Fig. 2 u. Fig. 4.)

Ich konnte sogar bei jüngeren Tumoren, die 13 Tage nach der Transplantation untersucht wurden, dem Bilde von beginnendem Stadium der Sarkomentwicklung begegnen, in denen ein allmählicher direkter Uebergang der Carcinomzellen zu den Sarcomzellen sicher festgestellt wurde: hier werden nämlich Krebsalveolen nach einer Richtung hin allmählich schmal-lang, bandartig; dementsprechend verlängern sich auch Zellleib und Zellkern und werden endlich spindelförmig, um mit den dazwischen auftretenden

Bindegewebsfibrillen schliesslich eine rein sarkomatöse Gewebsstruktur zu zeigen. (PLATE III. Fig. 3. u. 4.)

Weitere Veränderungen bei der Transplaptaion von Tumorstückchen, das neben Carcinomgewebe auch gleichzeitig Sarcomgewebe enthielt, sind sehr interessant: in diesem Fall finden wir, daß sich häufig nur Carcinomgewebe entwickelt, oder das Bild vom beginnenden Stadium der Sarkomentwicklung wiederholt wird. Bis wir reines Sarcom gewinnen, müssen wir mehrere Generationen von gemischter Form des Karzinoms und Sarkoms durchlaufen. Wenn die beiden Formen von Tumoren zwei verschiedene Ursprünge haben, d. h. einen epitheliale und einen anderen bindegewebiger Natur, so können sie sich bei weiteren Transplantationen ganz leicht in zwei verschiedene Richtungen differenzieren.

Die Grenze der beiden Gewebe in gemischter Form ist manchmal scharf, manchmal, wie schon oben erwähnt, ganz allmählich übergehend. Im ersten Falle scheinen beide Gewebe verschiedene Ursprünge zu haben. Aber wenn man den ersten Beginn von Sarkomentwicklung untersucht, so findet man niemals eine scharfe Abgrenzung zwischen beiden Geweben, die allerdings mit der Zeit schärfer abgegrenzt werden, indem sie nach verschiedenen Richtungen isoliert wachsen.

Wie die anderen Forscher beobachtete ich auch die Proliferation von interstitiellem Bindegewebe: das interalveolare Bindegewebe wuchert zuweilen sehr stark, dringt baumartig zwischen die Krebszellen ein, sodass diese gewucherten jungen Bindegewebszellen, Fibroblasten, in einigen Fällen von den spindelförmig veränderten Krebszellen kaum differenziert werden können. Ich denke, dass diese Bindegewebsproliferation die wichtigste Grundlage der Reiztheorie ist, die von vielen Autoren behauptet wird. Aber sie wird nach meiner Untersuchung durch die biologische Untersuchung, bes. die vitale Färbung leicht als unrichtig erkannt.

Vor der Erörterung der vitaler Färbung vergleiche ich kurz die Beschaffenheiten des Carcinoms und aus demselben entstand-

enen Sarkoms. Die Oberfläche des Karzinoms ist häufig granuliert bes. bei der Proliferation von interalveolarem Bindegewebe, während sie bei reinem Sarkom immer glatt ist. Auch ist zu beachten, daß die Nekrose innerhalb des Carcinoms stets in Zentrum und äusserst frühzeitig eintritt, dagegen in dem Sarcom ganz geringfügig in späterer Zeit zerstreut herdweise gefunden wird.

Die vitale Färbung.

Um die oben erwähnten Befunde zn bestätigen, habe ich die vitale Karminspeicherung angewandt. Die bisherigen morphologischen Untersuchungsmethoden, bzw. Gitterfaserfärbung, u. a., können niemals sicher die Natur der Zellen entscheiden. Die gegenwärtig beste Methode, durch welche man die epitheliale oder mesenchymale Natur der Geschwulstzellen entscheiden kann, dürfte wohl die vitale Färbung sein. Nach Prof. *Kiyonos* diesbezüglichen grundlegenden Untersuchungen sollen nämlich Zellen, welche irgendwie mesenchymalen Ursprung haben, stets Karmingranula speichern, während sämtliche Zellen epithelialer Natur mit einigen Ausnahmen, wie Leberzellen, Nierenepithelien u. a., ganz und gar dieses Charakters entbehren. Die Resultate meiner Untersuchungen ergeben folgendes: Die fast typische sarkomatöse Gewebsstruktur wurde durch spindelige Tumorzellen gebildet, die ganz gleich wie die ursprünglichen Krebszellen keine Karmingranula speicherten, während die histiozytären Zellen in die nekrotischen Herde sogar tief in das spindelzellensarkomartige Gewebe (aber niemals in den Krebsalveolen selbst) eindrangen und zahlreiche grobe Granula im Zelleibe speicherten. Ausserdem nahmen die gewucherten interalveolären und kapsulären Bindegewebszellen, d., h., Fibroblasten, stets schön feine Granula im Zelleibe auf.

Wenn also meine in Frage stehende sarkomartige Geschwulst, wie *Ehrlich* u. *Apolant* u. a. behaupteten, bindegewebiger Natur wäre, so müssten die Geschwulstzellen Karmingranula so gut wie

die Fibroblasten speichern; Mein diesbezügliches Resultat fiel jedoch negativ aus. (TAFAL III. Fig. 1. u. 2.)

Die Oxydasen-Reaktion der Geschwulstzellen wird auch mit α-Naphtol und Dimethylparaphenylendiamin nach *Katsunuma*scher Methode untersucht. Die spindelzellensarkomartigen Tumorzellen zeigten gleich wie die ursprünglichen Krebszellen deutliche positive Reaktion. Andere Geschwulstzellen, die ich untersucht habe, Fibrosarcom (Epulis) Osteoblastisches Sarcom, Chondromzellen bei der multiplen carcilaginären Exostose, myelogenes Sarcom, zwei Fälle von ileocoecalem Rundzellensarcom(?), Cancroid, Adenocarcinome des Magens und Darmes, zeigten alle stark oder schwach positive Oxydasenreaktion. Nur in einem Falle von einem aus der Subcutis ausgegangenen Spindelzellensarcom fiel dieselbe negativ aus.

Zusammanfassung.

1) Ich beobachtete die Erscheinung von sog. Sarcomentwicklung bei der Transplantation von Mäusekrebs, und zwar unter meinen 180 Impftumoren 24 Fälle von gemischten Formen, 8 Fälle von rein spindelzellensarcomartigen Tumoren, von welch letzteren sogar ein Fall sich bis jetzt zu weiteren Generationen als solcher gut transpantieren liess.

2) Das innerhalb des implantierten Mäusekrebses entstandene spindelzellensarkomartige Gewebe ist nichts anderes als das modifizierte Karzinomgewebe, das sich nur morphologisch, aber keineswegs biologisch sarkomatös umgewandelt hat.

3) Aus diesem Grunde möchte ich weiter vermuten, daß gelegentlich auch beim Menschen solche Geschwülste vorkommen können, welche morphologisch irgend ein Sarcombild darbieten, und deshalb auch klinisch als Sarcom diagnostiziert werden, während in Wirklichkeit nichts anderes als ein modifiziertes Karzinom vorliegt.

Erklärung der PLATE III.

Fig. 1. (K. 24. A. 1) Vergrösserung 200:1.
140 Tage nach der Impfung; gemischte Form von Carcinom und Sarcom, bindegewebig scharf begrenzt.

Fig. 2. (Nr. 83. 2.) Vergrösserung 200:1.
Sog. Spindelzellensarcom in früherer Generation. Vergleich TAFAL I.

Fig. 3. (Nr. 96. 7.) Vergrösserung 55:1.
Das Bild von Sarcomentwicklung im ersten beginnenden Stadium.

Fig. 4. (Nr. 106. 9.) Vergrösserung 200:1.
Wiederholt geimpftes reines sog. Spindelzellensarcom.

Fig. 5. (Nr. 96. 7.) Zeiss Okular 2. Objektiv DD.
K. Krebsalveolen, S. spindelförmig veränderte Krebszellen zeigen sarcomartiges Aussehen.

The Effects of the Lanoline-Feeding upon the Growth of the transplanted Chicken-Chondroma.

By

Dr. **Nobumaro Akamatsu.**

(*From the Pathological Laboratory of the Medical Department of the Imperial University, Kyoto*)

The question with the author has taken for study in this experiment is whether the growth and the transplantability of tumor cells is influenced by a supply of lanoline as a diet to the fowls. In planning this experiment, the author has attempted to compare susceptibility and rate of growth of the transplantable chondroma inoculated into fowls, which have been on a lanoline-free or a lanoline-added diet. So the fowls used in this experiment were grouped into two lots, one of them being fed on an usual diet with addition of lanoline and the another without any addition of lipoids as controls. The tumor used for inoculation is a transplantable chondroma found by Dr. Kato in the Patho-

logical Laboratory in Kyoto. The experiments were repeatedly performed.

From the results of these experiments the author may infer: (1) That the rate of growth of transplanted tumors in the fowls fed with lanoline containing diets show a remarkable acceleration in comparison with those in lanoline-free lot. (2) That the histological features of the tumors in lanoline-lot become more atypical morphologically, showing a marked proliferation of fibroplastic tissue and an increased mucoid degeneration, while the tumors in lanoline-free lot remained almost unchanged in biological and morphological characters.

As regards to the accerelated condition of the growth of the tumors in lanoline-lot, which is almost identical with the results obtained in the two previous experiments performed by him, the author concluded that these morphological and biological changes in tumor cells were caused by the unusually altered general condition of fowls due to lanoline-feeding.

(*T. K.*)

A Case of the Primary Hepatic Carcinoma in a Child.

By

Dr. **Masateru Takaidzumi.**

(*From the Pathological Laboratory of Medical College, Niigata.*)

Carcinoma derived from the liver cells has been considered to be comparatively rare in children. The author reported a case of this tumor, which was found in a boy, 9 years aged.

Gross description: Liver, Size 27 × 22 × 10 cm., Weight 1975 gms. The organ was considerably enlarged, and multiple

grayish white coloured nodules of various sizes (miliary-bean-walnut-goose egg) were noticed on its surface. On cut-surface, the right lobe of the liver was largely replaced by massive tumor tissues and the compressed and atrophied liver substance was merely observed in peripheral portion.

In the central portion of this tumor, there was a scarified and fibrous encapsulated pea-sized nodule of yellowish gray-white colour, which was considered as a primary growth by the author.

Scattered throughout the liver substance of the above mentioned atrophically remained portion in the right lobe and in the left lobe, there were numerous smaller secondary nodules of various sizes to be found.

These nodules were coloured yellowish or reddish gray white and hemorrhagic in places, and partially encapsulated with fibrous tissue or directly surrounded by liver substance. The tumor parenchym was divided into islets of various sizes by the fibrous bands radiated from the surrounding fibrous capsules. Tumor-thrombosis in intrahepatic veins and in vena cava inferior was recognized, and periportal lymph node was enlarged due to the tumor metastasis. Nothing of important changes in the biliary ducts and gall bladder were found. Several metastatic nodules in both lungs were confirmed.

Histological characters of this tumor showed a typical feature of the liver-cell carcinoma. In this case, the author reported that there was also simultaneously observed a condition of cholesterinaemia in the patient.

(*T. K.*)

Über den therapeutischen Wert der Tumorsubstanz bei transplantablen Mäusekarzinomen.

Von

Dr. **Makoto Takahashi.**

Von der biologischen Seite wurden therapeutische Versuche an geimpften Mäusekarzinomen von zwei Arten („63" und „*Twort*" aus Imperial Cancer Research Fund, London) in folgenden Versuchsreihen angestellt.

1. Therapeutische Versuche mit einem Filtrat, welches aus einer 1% igen Kochsalzlösungsemulsion des nekrotischen Teils der Mäusekarzinome dargestellt ist. An Mäusen, welche schon einen geimpften Tumor von 0,3 bis 1 cm. Durchmesser trugen, wurde 0,3 bis 0,4 ccm des Filtrats intravenös in eine Schwanzvene oder 0,5 bis 0,6 ccm unter die Rückenhaut eingespritzt. Bei Karzinom „63" wuchsen die Tumoren an den Versuchstieren ohne Störung in ca. 77% von den positiv geimpften Fällen, während sie sich an den Kontrolltieren in ca. 91% von den positiv Geimpften gut entwickelten. Bei Karzinom „Twort" war der Prozentsatz an den Versuchstieren 72%, während er an den Kontrollen 83% betrug.

2. Therapeutische Versuche mit dem filtrierten Tumorautolysat.

Tumoren wurden zuerst zerkleinert und dann 24–72 Stunden lang in die physiologische Kochsalzlösung gebracht, im Eisschrank, gelegt, damit die Autolyse gut vor sich ginge. Die Emulsion wurde dann durch einen Pumpenfilter filtriert und das frische klare Filtrat zum Versuch gebraucht.

Die wiederholten subkutanen Verabreichungen hatten hier auch eine hemmende Wirkung auf das Wachstum der geimpften

Tumoren ohne Störung der Gesundheit des Versuchstieres. Bei Karzinom „63" wuchsen die Tumoren an den Versuchstieren gut in 62% von den positiv Geimpften, während der Prozentsatz an den Kontrollen 91% betrug. Bei Karzinom „Twort" war das Verhältnis durchschnittlich 67% zu 83%

3. Therapeutische Versuche durch subkutane Einsteckung des erhitzten Tumorstückchens:

a) Einfluss der subkutanen Einsteckung des erhitzten Tumorstückchens auf das Resultat der nachfolgenden Tumorimpfung.

Ein Stückchen (ca. 0,05 gr.) des Tumors wurde ausgeschnitten und bei 50°C. 30 Minuten lang erhitzt, damit das Tumorstückchen unter möglichst geringer Beeinträchtigung der Tumorsubstanz der Wachstumsenergie beraubt würde.

Erst zwei Wochen nach der Vorbehandlung wurde an denselben Tieren eine neue gewöhnliche Tumorimpfung vorgenommen und der Einfluss der Vorbehandlung auf das neue Impfresultat beobachtet. Bei Karzinom „63" betrug an den vorbehandelten Tieren der Prozentsatz von positivem Ansfall der Impfung nur 60% gegenüber 96% an den Kontrollen. Bei Karzinom „Twort" war das Verhältnis noch deutlicher, und zwar 40% zu 93%.

b) Behandlung der geimpften Tumoren mit dem erhitzten Tumorstückchen derselben Art.

An den tumortragenden Tieren wurde subkutan ein in genannter Weise erhitztes Tumorstückchen eingesteckt und dessen Einfluss auf das weitere Wachstum des Tumors beobachtet. Bei Karzinom „63" war die Beeinflussung nicht deutlich, und zwar an den Versuchstieren wuchsen die Tumoren ohne Störung in 83% von den positiv Geimpften, während an den Kontrollen der Prozentsatz von 91% resultierte. Bei Karzinom „*Twort*" zeigte sich ein deutlicher Unterschied zwischen den Versuchs- und Kontrolltieren, und zwar im Verhältnis von 67% zu 83%. Der Grund der geringfügigen Beeinflussung des erhitzten Tumor-

stückchens bei Karzinom „63" liegt wahrscheinlich darin, dass bei diesem Typus der Tumor zu schnell gewachsen war, um die Immunität durch das vorangeimpfte, erhitzte Tumorstückchen ausreichend hervorrufen zu können. Die oben gezeigten Versuche ergeben, dass die Geschwülstsubstanz von Mäuseimpftumoren irgend einen Bestandteil enthält, welches eine hemmende Wirkung auf das Wachstum eines Tumors von derselben Art ausübt oder an den Impftieren eine Immunität hervorrufen kann. Auf welche Weise solche hemmende Wirkung durch Geschwulstsubstanz oder durch Immunisierung zu vervollkommnen, ist nicht wertlos weiter zu studieren.

(*Autoreferat.*)

Die Einflüsse der Keimdrüsen auf die Empfänglichkeit und das Wachstum des transplantablen Mäusekrebses.

Von

Tameyoshi Asada.

(*Aus dem pathologishen Institut der Kaiserl. Universität zu Fukuoka, Japan.*)

Beasten hat im Jahre 1896 gegen inoperable Mammakrebse die Kastration versucht. Er ging von der Idee aus, daß die Epithelwucherung des Körpers von dem Zustande der Keimdrüsen abhängig sei; Epithelwucherung in einer gesunden Brustdrüse führe zur Milchproduktion, in einer Kranken zur Krebsentwicklung. Die Kastration erzeuge fettige Degeneration und Untergang der gewucherten Krebszellen in ähnlicher Weise wie bei Kühen durch rasch aufeinander folgende Schwangerschaften oder durch Kastration der fettige Zerfall der Brustdrüsenepithelien stattfinde, und damit die Milchproduktion längere Zeit unterhalten werde.

Cahen hat 1909 berichtet, daß ein guter Erfolg in einigen unter 7 Fällen von Mammakrebs durch Kastration erzielt wurde und nach seiner Erfahrung bei einer jüngeren Patientin mit Brustdrüsenkrebs die ausgiebige Operation der Geschwulst durch die Kastration ergänzt und unterstützt wurde. Aber er bemerkt zuletzt, daß

ein grosser Teil der Brustdrüsenkrebse jenseits der Menopause auftritt, also, zu einer Zeit wo die Funktion der Ovulation erloschen ist; ob damit auch jede innere Sekretion der Ovarien aufhört, ist allerdings heute nicht zu entscheiden.

Graf. R. (1909) hat berichtet, daß kein wesentlicher Unterschied im Angehen und Wachstum des transplantablen Carcinom und Sarcom (hoch virulenter Tumor von *Ehrlich*) zwischen Kastrierten und den Kontrolltieren beobachtet wurde. *Rhodenburg, Bullock* und *Johnston* (1911) beobachteten, daß die Empfänglichkeit der Ratte gegen *Flexner-Jobling*'sches Carcinom durch Kastration herabgesetzt wurde. *Swect, Ellen P. Corson-White* und *Saxon* (1913) haben festgestellt, daß die Empfänglichkeit und der Wachstumsgrad des implantierten Tumors durch Kastration gefördert werden, und noch mehr der Wachstumsgrad durch Menge und Art der Nahrung positiv oder negativ beeinflusst wird. Es ist bemerkenswert, daß bei diesem Experimente die Impfausbeute des Maustumors ca. 40%, die des Rattentumors ca. 30% bei Kontrolltieren ist, also Virulenz schwächer ist als bei bisher untersuchten Tumoren, welche niemals durch Kastration in bezug auf Empfänglichkeit und Wachstumsgrad gefördert wurden. *Koreutschewsky, W. G.* (1913) konnte durch Kastration und Thyreoidektomie die bessere Ausbeute und ein rascheres Wachstum der Tumoren bei der Verimpfung des Rundzellensarcom beim Hunde beobachten. *G. Johannovics* (1916) hat bei dem *Ehrlich*'schen hoch virulenten Carcinom, Sarcom und Chondrom beobachtet, daß mindestens bei Carcinom die Kastration hemmende Einflüsse auf das Wachstum hat.

Da trotz dieser zahlreichen Untersuchungen über die Relationen der Keimdrüsen zu Tumoren bis jetzt noch keine Vereinigung erzielt wurde, machte ich zahlreiche Untersuchungen um diese Frage zu lösen.

Versuch.

Meine Versuche wurden, in drei Serien geteilt, vom September 1920 bis Januar 1922 ausgeführt. Die Untersuchungsmaterie ist ein zufällig in unserem Institute entdecktes Adenocarcinom der Maus, welches bis jetzt mit 50 prozentiger Impfausbeute sich gut transplantiert, aber wie in dieser Zeitschrift von mir beschrieben ist, sog. Sarcomentwicklung in allen Impfgenerationen erfährt.

Die Keimdrüsen wurden beim Männchen extraperitoneal durch Querschnitt des Scrotums nach der Unterbindung des Samenstrangs entfernt, beim Weibchen durch den Lateralschnitt entfernt, der entlang der Wirbelsäule unterhalb des Rippenbogens

doppelseitig ausgeführt wurde. Nach meinen zahlreichen Erfahrungen ist die Mortalität der Tiere äusserst gering.

Reiskorngrosse frisch bereitete Tumorstückchen wurden in die Subcutis des Rückens mit Troikart geimpft. Zur Messung des Wachstumsgrades von übergeimpften Tumorstückchen habe ich drei Wachstumsgrade angegeben: erstens, 30 Tage nach der Transplantation über Zeigefingerspitzgrösse erreichend, zweitens, von kleinfingerspitz- bis zeigefingerspitzgross, drittens, unter der Kleinfingerspitzgrösse, und ausserdem eine hypoplastische Form wenn der geimpfte Tumor bis erbsengross bleibt.

Versuchsserie 1. (Vom September 1920 bis März 1921) Hauptsächlich jüngere Tiere.

TAFEL I.

	Versuchs-Tiere.	Positive Fälle	Impfprozente.
Kastration	180 —m. 136 —w. 44	40 —m. 21 —w. 19	22.2% —m. 15.4% —w. 43.2%
Kontrolle	214	32	14.8%

TAFEL II.

Wachstumsgrad	I. Gr.	II. Gr.	III. Gr.	Hypo. F.
Kastration	5.	16.	18.	1.
Kontrolle	1.	10.	18.	3.

Wie man aus Tafel 1. ersehen kann, beträgt die Impfausbeute der Kastraten 22.2% (bei Männchen 15.4%, bei Weibchen 43.2%), die der Kontrolltiere nur 14.8%. Dementsprechend haben die Kastraten grössere Wachstumsenergie als die Kontrolle, d. h. bei den ersteren: Wachstum I. Grades 5, II. Grades 10, dagegen bei den letzteren I. Grades nur 1, II. Grades 10. (Tafel II). Wenn man

bei den Kastraten die Impfausbeute des Männchens und Weibchens vergleicht, so sieht man, daß sie beim letzteren auffallend günstiger ausfällt.

In dieser 1. Versuchsserie zeigt der Mäusekrebs unseres Falles äusserst niedrige Impfausbeute (gewöhnlich 50%), gleichzeitig herabgesetzte Wachstumsenergie. Die Ursache besteht darin, daß in dieser Zeit die schon erwähnte Erscheinung von sog. Sarkomentwicklung häufig eingetreten war.

Ich will noch hinzufügen, daß wie andere transmissible Tumoren auch bei unserem Fall die Impfung leichter bei jüngeren Tieren als bei Erwachsenen gelingt. Diese Tatsache ist wohl schon aus der Versuchsserie I. zu ersehen: der Unterschied der Impfausbeute und Wachstumsenergie zwischen den Kastraten und Kontrollen ist nämlich deutlicher bei postpubertaler Impfung, während er bei präpubertaler Impfung kaum nachweisbar ist, d. h. der wesentliche Unterschied besteht bei der postpubertalen Impfung.

Versuchsserie II. (Vom Mai bis Oktober 1921) Hauptsächlich erwachsene Tiere; der Zeitraum bis zur Impfung nach der Kastration viel länger.

TAFEL III.

	Versuchstiere	Positive Fälle	Impfprozente
Kastration	106 —m. 73 —w. 33	67 —m. 45 —m. 22	63.3% —m. 61.6% —w. 66.6%
Kontrolle	146	77	52.8%

TAFEL IV.

Wachstums grad	I. Gr.	II. Gr.	III. Gr.	Hypo. F.
Kastration	33	13	20	1
Kontrolle	29	20	28	0

Aus den Tafeln ersieht man, daß fast gleich wie in Serie I die hoch gesteigerte Impfausbeute und Wachstumsenergie bei den Kastraten besonders bei Weibchen gegenüber den Kontrolltieren sich zeigt. Als Ursache, warum in dieser Versuchsserie der Unterschied geringer als in der ersten ist, muss ich annehmen, daß die nach der Kastration lang überlebten Tiere im Sommer untersucht wurden, wo die Geschwülste immer höhere Virulenz als im Winter zu zeigen pflegen. Weiterhin wurde die Tatsache, daß der Unterschied deutlicher bei postpubertaler als bei präpubertaler Impfung ist, in Versuchsserie II einwandfrei konstatiert.

Versuchsserie III. (Vom Oktober 1921 bis Januar 1922) Dieses Mal habe ich, um die Tatsachen zu bestätigen, welche die Serie I u. II zeigten, hauptsächlich die erwachsenen Tiere untersucht, welchen bald nach der Kastration geimpft wurde. Dabei müssen die Kontrolltiere natürlich unter ganz gleichen Bedingungen stehen, da Alter, Zahl der Tiere (auch die Zahl der beiden Geschlechtern) Nahrung, Geburtsort, Beschaffenheit der zu impfenden Tumorstückchen, Impfmethode etc. das Tumorwachstum beeinflussen.

TAFEL V.

Fall		Vers. Tiere	Posit. Fäll.	Prozent	I Gr.	II Gr.	III Gr.	Hyp. Form
XXXVI	Kastration	9 (m. 4 w. 5)	5 (m. 3 w. 2)	55.5%	4	1		
	Kontr.	8 (m. 4 w. 4)	5 (m. 2 w. 3)	62.5%	1		4	
XXXVII	Kast.	6 (m. 3 w. 3)	1 (m.)	16.6%			1	
	Kont.	7 (m. 4 w. 3)	1 (m.)	14.3%			1	
XXXVIII	Kast.	7 (m. 2 w. 5)	6 (m. 2 w. 4)	85.7%	1	3	2	
	Kont.	5 (m. 3 w. 2)	2 (m. 1 w. 1)	40.0%		1	1	

XXXIX	Kast	9 (m. 4 w. 5)	9 (m. 4 w. 5)	100%	2	3	3	1
	Kont	8 (m. 4 w. 4)	5 (m. 3 w. 2)	62.5%	1	2	2	
XL	Kast	6 (m. 3 w. 3)	4 (m. 2 w. 2)	66.6%		1	3	
	Kont	6 (m. 3 w. 3)	4 (m. 3 w. 1)	66.6%	1		3	
XLI	Kast	6 (m. 1 w. 5)	5 (m. 1 w. 4)	83.3%	2	3		
	Kont	4 (m. 3 w. 1)	1	25.0%	1			
XLII	Kast	3 (m.)	1	33.3%			1	
	Kont	3 (m.)	0	0%				
XLIII	Kast	7 (m. 3 w. 4)	6 (m. 3 w. 3)	85.7%	4	1	1	
	Kont	9 (m. 4 w. 5)	5 (m. 4 w. 1)	55.5%	1	2	1	
XLIV	Kast	7 (m. 3 w. 4)	7	100%	7			
	Kont	7 (m. 3 w. 4)	4 (m. 1 w. 3)	57.1%	1	2	1	
XLV	Kast	6 (m. 2 w. 4)	4 (m. 1 w. 3)	66.6%	1	3		
	Kont	9 (m 5 w. 4)	3 (m. 2 w. 1)	33.3%	1	1	1	
XLVI	Kast	9 (m. 3 w. 6)	8 (m. 3 w. 5)	88.8%	2	1	4	1
		10 (m. 9 w. 1)	8 (m. 7 w. 1)	80.0%	1	2	5	

Gesammt

		positiv
Kastration	75	56....74.0%
Kontrolle	76	38....50.0%
—m.	28	23....82.1%
Kastration—w.	47	33....70.1%
Kontrolle—m.	42	25....59.5%
—w.	34	13....38.2%

Wachstumsgrad	I.	II.	III.	Hyp
—Kast....	23	16	15	2
—Kont....	7	10	20	1

Aus Tafel V ersieht man, daß bei den Kastrierten nicht nur die Impfausbeute um 24.6% höher als die der Kontrolltiere ist, sondern die transplantierten Tumoren auch eine enorm gesteigerte Wachstumsenergie haben. Dieser Unterschied zwische den Kastraten und Kontrolltieren ist noch deutlicher bei Weibchen als bei Männchen, nämlich bei den ersteren um 31.9%, bei den letzteren um 22.6% höher als die Kontrolle.

Vergleicht man zunächst die Impfausbeute und Wachstumsenergie in jedem Alter, welches durch das Körpergewicht (Gramm) bezeichnet wird, so sieht man wesentliche Unterschiede bei der postpuberalen Impfung. Bei japanischen Mäusen tritt die Pubertät in dem Alter von 9 bis 10 Gramm-Körpergewicht ein.

Zusammenfassung.

1. Die Kastration brachte in 22 unter 46 Fällen, die, in drei Versuchsserien geteilt, vom September 1920 bis Januar 1922 untersucht wurden, eine erhöhte Impfausbeute zustande gegenüber den Kontrolltieren, während sie bei Kontrolltieren in 11 Fällen höher, in 13 Fällen der Unterschied weniger als 5% ist.

2. Unter 361 Kastraten betragen positiv geimpfte Tiere 163 d. h. 45.1%, bei 436 Kontrollen 147 d. h. 33.7%.

3. Bei den Kastraten findet sich Wachstum I. Grades 61 (37%), II. Grades 45 (27%), III. Grades 45 (27%), hingegen bei den Kontrollen I. Grades 37 (25%), II. Grades 38 (26%), III. Grades 68 (46%) Fälle; die hypoplastischen Formen sowohl bei Versuchs- als auch Kontrolltieren 3% der Fälle.

Wie wir aus diesen Resultaten ersehen können, ist es zweifellos, daß die Impfausbeute und gleichzeitig die Wachstumsenergie durch die Kastration erhöht wird. Wir wollen noch weiter nach der Ursache forschen, warum die Resultate von vielen Forschern sich noch nicht decken. Ich werde daher noch die Bedingungen berücksichtigen, die nach meinen Untersuchungen die Impfresultate beherrschen:

1. Das Geschlecht. Nach meinen Untersuchungen beträgt die Impfausbeute bei den männlichen Kastraten 53.0%, bei den männlichen Kontrollen 46.8%, während sie bei den weiblichen Kastraten 60.0%, bei den weiblichen Kontrollen 32.1% beträgt. (durchschnittliche Werte von drei Versuchsserien). Demnach kann man behaupten, daß beim Weibchen der Unterschied deutlicher als beim Männchen ist.

2. Alter. Wie ich schon oben erwähnte, treten die wesentlichen Unterschiede der Impfausbeute und Wachstumsenergie zwischen Kastraten und Kontrolltieren ausnahmslos bei allen drei Versuchsserien nur bei der postpubertalen Impfung auf.

3. Periodische Schwankung von Tumorvirulenz. Diese Erscheinung ist schon von vielen beobachtet, nämlich eine Steigerung der Wachstumsenergie und der Impfausbeute im Frühling und Sommer, dagegen ein Sinken im Herbste und Winter. Im gleichen Sinne steigerten sich auch in unseren Fällen bei Kontrolltieren vom März bis Oktober Wachstumsenergie und Impfausbeute durchschnittlich über 60% (ausnahmsweise im Juli 27%), während sie vom November bis Februar durchschnittlich unterhalb 40% herabsinken. Ich fand eine sehr merkwürdige Tatsache, daß bei den Kastraten die Tumorvirulenz durch die Jahreszeit nicht beeinflusst wurde, sondern stets erhöht war. So nehme ich an, daß die Ursache der periodischen Schwankung der Tumorvirulenz irgendeinen Zusammenhang mit der Funktion der Keimdrüsen hat. Weiter fand ich die Tatsache, daß der Unterschied der Impfausbeute und Wachstumsenergie von Tumoren zwischen dem Kastraten und Kontrolle im Winter deutlicher ist, wenn nämlich die Kontrolltiere eine schwächere Virulenz zu ergeben pflegen, während im höher impfbaren Sommer kaum ein Unterschied zu konstatieren ist. Daher kann man sagen, daß die Untersuchung mit den hoch virulenten Tumoren, wenn diese zu einer eine hohe Virulenz begünstigenden Jahreszeit eingeführt werden, stets negativ ausfallen wird.

4. Auch der Zeitraum zwischen Kastration und Impfung beherrscht die Untersuchungsresultate. Ein deutliches positives Resultat wurde nur bei den nach der Kastration früh geimpften Fällen erhalten, gewöhnlich 1–2 Wochen nach derselben, dagegen fiel das Resultat nach mehr als 30 Tagen stets negativ aus. Auf diesem Grunde möchte ich behaupten, daß der Einfluss der Keimdrüsen auf Tumorimpfung und -wachstum durch nichts anderes als ihre insere Sekrete selbst bedingt wird, und die sekundären Veränderungen des Organismus, welche durch die Kastration mit der Zeit entstehen nicht in Betracht kommen.

Schluss.

1. Die innere Sekretion der Keimdrüsen hat eine hemmende Wirkung auf die Transplantabilität und das Wachstum des transplantablen Mäusekrebses, sodass durch die Kastration die Impfausbeute und die Wachstumsenergie erhöht werden.

2. Die Untersuchungsresultate werden durch verschiedene Momente beherrscht, erstens das Geschlecht der Kastraten, zweitens das Alter, d. h. präpubertale oder postpubertale Impfung, drittens die periodische Schwankung von Tumorvirulenz und die biologichen Eigenschaften von transplantablen Tumoren, viertens den Zeitraum zwischen Kastration und Impfung.

3. Die periodische Schwankung der Tumorvirulenz hat wahrscheinlich irgendeinen Zusammenhang mit der periodischen Steigerung der Keimdrüsenfunktion.

4. Bei der Entstehung von primären Tumoren, besonders von Carcinom, dürften wohl nicht nur bei Tieren, sondern vermutlich auch beim Menschen die Keimdrüsenfunktionen irgendeine Rolle spielen.

Über die Karzinommetastase an den Zirkulationsorganen.

Von

Dr. **Katsushiro Eguchi.**

(*Aus dem pathologischen Institut des Izumibashi-Hospitals.*)
(*Direktor: Prof. Dr. M. Fukushi*)

(Mit TATEL IV.)

Die Zirkulationsorgane spielen als eine metastatische Bahn der Geschwulstzellen und in Bezug auf ihre Entwickelung oder Entartung eine wichtige Rolle. Aber die Geschwulst, die sich aus der Gefässwand selbst primär oder sekundär entwickelt, ist sehr selten. Lassen wir nun zuerst die wichtigsten diesbezüglichen Literaturen, vorangehen.

A) Die Geschwülste aus den kleinen Gefässen:

a. Gutartige Geschwülste:

1. Angioma simplex.
2. Angioma spongiosum.
3. Angioma lacenosum.

b. Bösartige Geschwülste:

1. Hämoangioendotheliom.
2. Perithelioma. (Angiosarcom)

Zu dieser Gruppe gehören die Geschwülste, welche sich nicht aus dem partiellen Gefässbestandteile entwickeln, sondern eine abnorme Wucherung des gesamten Organes darstellen.

3. Sonstige Geschwülste:

Eine häufige Beobachtung ist das Auftreten der embolischen Metastase der malignen Geschwulstzellen (z. B. bei Karzinom, Sarkom, malignem Cholionepitheliom, u. s. w.) in den peripherischen Arterien, welche die Gefässwände im verschiedenen Grade zerstört.

B) Die Geschwülste aus dem Herzen:

a. Gutartige Geschwülste:

Als die primären sind Myxom (*Mink*, 1910), Myxofibrom (*Hanser*, 1912), und auch einige Fälle von Fibrom, Lipom, Lymphangiom, Rabdomyom u. s. w.; und als die sekundäre nur ein Fall von Rabdomyom (*Aschoff*) bekannt.

b. Bösartige Geschwülste:

Geipel (1899), *Binder* (1913), und *Wünschhaus* (1919) hatten schon Mitteilungen über je einen Fall von primärem Sarcom gemacht. Nach der Literatur metastasie-

eren häufig Neubildungen, bei Sarcom, Melanosarcom, Osteosarcom, Karzinom, u. s. w.: dabei ist die Metastase des letzteren relativ häufig.

C) Die Geschwülste aus den Arterien:

a) Gutartige Geschwülste:

Wir kennen keinen Fall von primärer oder sekundärer Geschwulst, ausser einem von Beckenchondrom (*Ernst*), welches durch die V. c. inf. die Pulmonalklappen erreicht, und da ein fingerspitzgrosses metastatisches Neoplasma bildete.

b. Bösartige Geschwülste:

Diese sind sehr selten. Wir kennen nur einige Fälle von dem primären Sarcom aus der Aorta (*Moriani, Brodowski, M. Miura, Auffermann*). Ausserdem gibt es 2 Fälle von sekundärem Sarcom an der Aorta thoracicus, welche *Moriani* und *Grützner* beobachtet haben. Über die Metastase des Karzinoms beschrieben *Buquoy* (1-Fall), *Rokitansky* (1-Fall), *Laucereaux* (1-Fall), *Zahn* (2-Fälle), und *Altmann* (4-Fälle). Alle diese Fälle sind die Metastase des Ösophaguskrebs. Ferner haben wir noch einige wichtige Berichte über das metastatische Karzinom an der Aorta und A. pulmonalis (*Volk, Förster, Ceelen, Warenher, Velpeau, Braca*).

D) Geschwülste aus den Venen:

a. Gutartige Geschwülste:

Es gibt nur einen einzigen Fall primären Neoplasmas, ein Myom, welches aus der Wandung der Vena cava inferior entstammt (*Aschoff*). Als Beispiel sekundärer Neubildung haben wir auch nur einen Fall vom metastatischen aus dem Becken entstammenden Chondrom in derselben Gefässwand.

b. Bösartige Geschwülste:

Es gibt nur 2-Fälle in der Literatur, ein primäres Hämoangioendotheliom aus der V. cava inferior und ein sekundäres Angiosarcom an demselben Gefäss, welches aus der Niere entstammt.

Über Karzinom berichtet *Warenher* einen Fall, wobei sich Geschwulstthrombus auf der Intimafläche der Hohlvene und ferner embolische Metastase in den Lungenarterien bildete.

Über die Entwickelungsweise metastatischer Geschwülste (besonders Karzinoms) in den Zirkulationsorganen können wir wie folgend zusammenfassen.

a. Thrombotische Metastase.

Derartiger Vorgang wird nach *Volk* durch die atheromatöse Entartung der Gefässwand und dazu die durch die Arteriosklerose verursachte Zirkulationsstörung beträchtlich gefördert.

b. Die Venenwand wird hauptsächlich zuerst von Adventitia angegriffen. Schreitet der karzinomatöse Prozess nach innen allmälich fort, so wird die Intima endlich verödet; und hierauf folgt Thrombenbildung oder seltener Perforation. (*Pucheit*)

c. An den Arterien geht zuerst eine Periarteritis vor sich, und an den

Venen entsteht Endophlebitis carzinomatosa, wobei die Verbreitungsweise der Vasa vasorum in Betracht kommt. (*Goldmann*)

d. Retrogradige Verschleppung durch die Lymphbahn (*Heller, Recklinghausen,*) oder das Venensystem (*Thorel, Riesel*).

An den Zirkulationsorganen ist jedoch im all die Geschwulstbildung, sowohl primär als auch sekundär, nicht so häufig.

Der Fall, den ich hier mitteilen werde, betrifft einen Pankreaskrebs, welcher im ganzen Zorkulationssystem eine ausgedelmte Metastase bildete.

Klinische Befunde:

Diagnose: Blasenkrebs, Urethrastenose.

65 j. Arbeiter, von Kindheit an ganz gesund. Vor 34 Jahren litt er angeblich an Gonorrhoe, welche nach 8 monatiger Behandlung fast geheilt wurde; und nachher verblieb ihm eine Beschwerde beim Harnabfluss. Er war ein grosser Raucher und Trinker. Er negiert streng luetisches Leiden. gegen September 1921 bemerkte er eine Anschwellung des Hodensacks, des Unterbauches bes. behaarten Teils und der Vorhaut des Penis. Angeblich ist eitrige Masse zuweilen aus der äusseren Mündung des Harnwegs ausgeflossen. Gleichzeitig sind einige der linken supraculavicularen Lymphdrüsen zumteil taubeneigross angeschwollen. Gegenwärtig klagt er hauptsächlich über hochgradigen Harndrang und starke Beschwerde beim Harnabfluss: Bei mikroskopischer und chemischer Harnuntersuchung bemerkt man Blutbestandteile, Eiweiss und Eiterkokken. Am 8. Mai 1922 wurde er in dieses Krankenhaus aufgenommen und starb am 5. Juni desselben Jahres.

Obduktionsbefunde:

1. Karzinom und karzinomatöse Geschwüre in der Harnblase.

2. Karzinommetastase in retroperitonealen-, beiderseitigen inguinalen-, linken achillaren-, linken supraclavicularen-, linken

Hals-, peribronchialen Lymphdrüsen und am Pankreaskopfe, dem rechten Nierenbecken, dem rechten Ureter und der Prostata.

3. Multiple Abszessbildungen in der rechten Niere und Nierenkapsel.

4. Pyonephrose dextra.

5. Infarktbildung in der linken Niere und der Milz.

6. Aortitis syphilitica.

7. Arteriosklerose.

8. Braune Atrophie des Herzens.

9. Pericarditis.

10. Partialles Emphysem, Stauung und Ödem in den beiden Lungen.

11. Bronchitis.

12. Pleuritis exsudativa duplex.

13. Peritonitis exsudativa.

14. Infektionsmilz.

15. Stauungskatarrh des Magens und Darmes.

Vor allem ist die Metastase an den retroperitonealen Lymphdrüsen am grössten, welche die ganze rechte Beckenhöhle ausfüllt. Noch bemerkenswerter ist es, daß A. et V. iliaca communis und A., V. iliaca ext. et int. dextra in die oben genannten gigantischen Tumormasse eingepackt und zwar mässig abgedruckt werden. Bei der makroskopischen Untersuchung muss man an diesem Fall, den primärer Herd in der Harnblasenwand suchen und alle anderen Tumoren ais metastatische Bildungen ansehen, welche durch die Lymph-und Blutbahn entstanden sind.

Mikroskopische Befunde:

1. Primäres Adenocarzinom am Pankreaskopfe.

2. Metastase an mehreren Lymphdrüsen um das Pankreas, besonders an den linken Hals-, linken supraclavicularen-, linken achillaren-, peribronchialen-, und retroperitonealen Lymphdrüsen.

3. Metastase am Herzen, an der Aorta in ihrem ganzen

Verlauf, teilweise von Adventitia bis zur Intima, an der beiderseitigen V. iliaca communis, rechten A. u. V. iliaca ext. et int., rechten A. femoralis, Vena cava inferior und linken A. et V. achsillaris.

4. Metastase in den Lungen, der Leber, der Milz, den beiderseitigen Nieren, der rechten Nierenkapsel, dem rechten Nierenbecken, dem rechten Ureter, der Harnblase, der Prostata und dem Rektum.

5. Infarktbildung in der linken Niere und der Milz,

6. Syphilitische Veränderung der gesamten Zirkulationsorgane, besonders Mesaortitis syphilitica.

7. Arteriosklerose.

8. Karzinomzellenembolie oder Thrombenbildung in den peripherischen Blutgefässen. z. B. im Herzen, in den Lungen, Nieren oder in den grossen Blutgefässwänden.

9. Karzinomatöse Ulzeration und Verschluss des rechten Ureters, und dadurch verursachte Pyonephrose dextra.

10. Multiple Abszesse der rechten Niere.

11. Syphilitische produktive Entzündung in den verschiedenen Organen.

Bei genauer Mikroskopierung der verschiedenen Organe, wird es festgestellt, daß der primäre Herd dieses Falles im Pankreaskopfe liegt, und die Harnblase, welche bei der makroskopischen Beobachtung wie der primäre Herd erscheint, tatsächlich der sekundäre metastatische ist. Für die Grundleiden dieses Falles halten wir Karzinom, Syphilis, Arteriosklerose, Es scheint, daß die Wege, auf welchem sich die Karzinomzellen verbreiteten, die Lymph- und Blutbahn sind. Zuerst scheinen die Karzinomzellen, die sich um Pankreaskopfe entwickelten, in den regionälen Lymphbahnen und Venen einzudringen, um weiter durch Plexsus cöliacus Ductus thoracicus, respektiv A mesenterica sup. V. porta, die Lebervenen und V. cava inf. das kleine Kreislaufssystem zu erreichen. Nach der Metastasebildung in den Lungen, treten die Zellen in den grossen Kreislauf hinein was zur allgemeiner Metastase führte. Die Metastase in den Gefässwänden ist eine Teilerscheinungen,

und der Prozess wird durch die syphilitische und sklerotische Veränderung der Gefässwände und die dadurch bedingte Zirkulationsstörung begünstigt wurde.

Schluss:

Betreffs der Metastasierung der Geschwülste, besonders des Karzinoms, an den Zirkulationsorganen kann ich nach meiner näheren Untersuchung wie folgend zusammenfassen.

1. Eindringen der Geschwulstzellen durch Vasa vasorum.
2. Retrogradige Verschleppung der Geschwulstzellen durch die Lymphbahnen.
3. Fortschreiten von den Nachbarschaften.
4. Von dem Thrombus der Intimafläche.
5. Abnahme der Gewebswiderstandfähigkeit, welche wegen der syphilitischen und sklerotischen Veränderungen hervorgerufen wird, und die gleichzeitige Zirkulationsstörung sind der wichtigste Modus für die Metastasenbildung.

(*Autoreferat.*)

Erklärungen des PLATE IV.

Fig. 1. Metasase an Media von Aorta.
Fig. 2. Metastase an Intima von Aorta.

Über ein Fall von Milzkarzinose.

Von

Dr. **Ikuya Honda.**

(Aus dem pathologischen Institute der med. Akademie zu Kyoto, Vorstand: Prof. T. Tsunoda.)

(Mit TAFEL V.)

In einem Fall von Krebs des rechten Oberkiefers bei einem 44 jährigen Mann, konnte Verfasser eine sehr seltene Veränderung in der Milz finden. Bei der Sektion liess sich folgendes feststellen.

1. Hornbildender Plattenepithelkrebs des rechten Oberkiefers mit ausgedehnter Infiltration in der Umgebung.
2. Metastasenbildung in den Bronchiallymphdrüsen, Lungenhiluslymphdrüsen, Lugengeweben (mikroskopisch) und der Leber (in einer kleinen Partie).
3. Bronchopneumonia catarrhalis.
4. Fragmentation und Atrophie des Herzmuskels.

Die Milz war etwas derb und vergrössert, wog 230 Gram. Auf der Schnittfläche insbesondere am Pulpagewebe sind weissliche Knötchen zerstrent vorhanden, was an einer Amyloidmilz erinnert.

Die mikroskopische Untersuchung der Milz liess eine interessante Veränderung derselben erkennen. Die *Malpigi*schen Körperchen waren wirklich überall gesund, und in den Zentralarterien waren keine Geschwulstthromben bemerkbar. Die Pulpa und der Venensinus waren überall mit dem Geschwulstgewebe infiltriert, welches aus kleineren kubischen, ovalen oder länglichen, zylindrischen Zellen mit chromatinreichen, intensiv gefärbten Kernen bestand. Verfasser konnte kein Verhornungszeichen trotz sorgfältiger Untersuchung ausfindig machen, sondern die Geschwulstzellen wiesen niedere Differenzierungsform als die Muttergeschwulst auf. Noch interessanter war es, dass in der Milz keine Reaktionswucherung

des Bindegewebs vorhanden war, und viele Plasmazellen und polymorphkernige neutrophile Leukocyten auftraten.

Was die Art und Weise der Metastasenbildung in der Milz anbetrifft, so ist eine lymphogene ohne weiteres auszuschliessen, da, wie bekannt, die Lymphbahn in der Pulpa vollständig fehlt. Es fragt sich also, ob die Milzmetastase auf der arteriellen oder venösen Bahn stattfand.

Auf Grund der Intaktbleiben der Lymphknötchen und der diffusen Infiltration der Geschwulstzellen in der Pulpa und im Milzsinus, neigt Verfasser der Ansicht der Retrogradmetastase durch die venöse Bahn.

(*Autoreferat.*)

Erkrärung der Abbildung. (PLATE V.)

L., Lymphknötchen. G, Geschwulstzellen im Milzsinus und Pulpagewebe.

On the maxillary and mandibular tumors in the horse. (Adamantinoma, Fibroma and Sarcoma.)

By

Dr. **Tetsuji Kimura**
and
Dr. **Seiichiro Taguma.**

(*From Pathological Laboratory of the Tokyo-Jikeikai Medical University.*)

(with PLATE VI.)

The authors dealt with three cases of tumors in this article, which arose from the upper and lower jaws of horses.

CASE I. Adamantinoma.

Macroscopical Features: The tumor sited on the lateral surface of the right mandible in a slaughtered horse, emerging

as a semisphere-shaped, somewhat sharply margined nodule of a fist size and of firm consistency. On its cut-surface was recognized the strands-like, opaque grayish-white or-yellow coloured parenchymatous tissue, which showed wavely convolutions and was irregularily mingled with grayish-white coloured stromatous fibrous tissue. No marked necrosis and no hemorrhage. Metastasis was nowhere recognized.

Microscopical Features: By low-power magnification, it was recognized that the tumor consisted of broad and irregularily anastomosing strands of epithelium and of fibrous connective tissue, showing a distinct alveolar structure. In peripheral portion of epithelial strands, there was a tubular or adenomatous structure of the parenchym-cells to be seen, showing the formation of a pallisade-like arrangement or a gland-like lumen.

The stromatous fibrous tissue was generally in weak developement. The most peripheral cells of parenchym-strands abutting on the stromatous connective tissue were fairly cylindrical in form (size 30–50 × 14–18 μ.), and their nuclei were situated away from the surrounding fibrous tissue instead of close to it, as was used in most other epitherial lined surfaces. The cells in central portion of the alveolar strands (size: 28 μ in dia.) became polyhedral in shape and loosely arranged due to the gradual separation of the cells, while no marked cavity-formation or accumulation of fluid was observed. There was no intercellular fibrillar substance among those parenchym-cells to be found, and a slight deposit of fat-granules was recognized in some cells of parenchymatous strands, which were loosely arranged in central portion of the alveoli.

As regards the histogenesis of the tumor, the authors concluded that this tumor derived from the cells of the enamel organ of epiblastic origin, having compared the macro- and microscopical features between the morphological characters of the tumor and the enamel organ. So this tumor is rightly called as Adamantinoma (Adamantoblastoma) or Odontoepithelioma.

CASE II. Fibroma (periostal Fibroma).

Macroscopical Characters: The tumor sited on the lateral side of the right under jaw, which was of about human head size and widely based on the bony substance. Consistency very hard and sharply margined. By section, it was found that a silky white dense fibrous bundles in irregular arrangement were seen on the cut-surface in various directions. No necrosis and no hemorrhagic infiltration. No metastasis.

Microscopical Characters: Histologically this tumor consisted of uniform fibrous tissue, differing in it's density. According to the compactness of the fibrous tissues it may possibly be divided into three various portions :—

1. A cellular portion mostly consisting of extremely elongated spindle-shaped young fibroblasts and fine delicate intercellular fibers weakly developed :

2. More densely composed fibrous portion with well developed intercellular fibrous substances, being diminished in number of cellular constituents :

3. Extremely loose fibrous tissue, consisting of weakly developed and loosely arranged delicate fibers, combined with comparatively numerous blood capillaries, though this portion appeared not so cellular.

Intercellular fibrillar substances were found generally throughout, especially in specimens of " Gitter-faser " staining with silverimpregnation by Bielschowsky they became much more distinctly recognizable.

According to the above mentioned histological features, it may be rightly considered that (1) corresponds to the young cellular parenchymatous constituent of this tumor, (2) to more matured fibrous portion of (1), and (3) may be recognized as the stromatous fibrous tissue combined with blood-vessels.

From these anatomical features and characteristic arrangement of tumor cells, showing much resembrance to those of the periostal

sarcoma, the authors inclined to consider that this tumor derived from the periostal fibrous tissue of mandibula and may be called as periostal Fibroma or Fibroblastoma.

CASE III. Spindle celled Sarcoma.

Macroscopical Examination: On the maxilla of a slaughtered stallion, 12 years aged, there was a destructive growing tumor of human head size and of somewhat firm consistency. On cut-surface it was noticed that grayish white medullary soft parenchymatous portion was divided into islets of various sizes by irregular stromatous fibrous tissue in varying widths. Dark reddish hemorrhages and grayish-white-yellow necrotic softenings scattered in places to be seen.

Histological Examination: The tumor was almost uniformly composed of much cellular fibroblastic tissue, differing merely in degrees of tissue-maturity and without any marked alveolar structure. The tumor cells were mostly polyhedral, short-spindle or oval in shape (size: 21 μ in dia.), and their nuclei also of oval or short-spindle form (size: 14 μ in dia. or 14–21 μ.,) numerous mitotic figures in diaster- or monaster-stage being observed. The relationship between the tumor cells and stromatous fibrous tissue was very intimate, and it was proved that intercellular fibrillar substances were distinctly recognized almost throughout.

Comparing these morphological characters of this tumor to those of already described cases by Kitt and other workers the authors thought that this tumor might be considered as Osteosarcoma or osteoblastic Sarcoma, which is one of most commonly observed tumors in horses. (*Authors' abstract*)

Description of PLATE VI.

Section of the tumor (Adamantinoma) in case 1.

Fig. 1. (Low power microphotograph).

Fig. 2. (High power microphotograph, silver impregnation by Bielschowsky's method).

Studies on the Metastasis of Chicken Sarcoma.

By

Kenji Tadenuma.

(*From the Iriuwa Clinic, Medical College, Imperial University, Tokio.*)

In the Gann, Vol. XII, No. 3, I reported that by bleeding a large amount of blood from chickens transplanted with chicken sarcoma (The second type of Fujinami and Kato's myxoma), the rate of metastatic formation is increased. The same fact has also been proved by Okonogi and myself with rat cancer, and we reported the result in the Gann, Vol. XV, No. 2. The present experiment is undertaken to clear under what conditions the metastatic formation is influenced. Of course, the factors are not simple, but it is prodcued by combined action of many influences. If, however, the influences caused by bleeding, such as decrease of blood corpuscles, changes of serum and circulation, are studied separatedy, there must be found some relation between the bleeding and metastatic formation.

As a first step I wished to find the influence of anemia which is a marked phenomenon caused by bleeding. For this purpose alcoholic solution of phenylhydrazine was injected into chickens transplanted with the sarcoma, and the rate of metastatic formation was compared with the control chickens. The same experiment was carried out with rat cancer conjointly with Okonogi.

Method of Experiment.

Various amounts of 1% phenylhydrazine alcoholic solution (10% alcohol water) were injected subcutaneously at different times to cause anemia in the chickens transplanted with the sarcoma. When the chickens died naturally, they were dissected and examined for metastatic formations macro. as well as microscopically.

Experiment I.

No.	Date of transpl'n	Date of Injection	Date of Death	Living Days	Site of Metastasis
1.	May 10. '21.	May 2, 2 cc.	May 24.	15	—
2.	,,	May 20, 25. 2 cc. each.	May 27	18	—
3.	,,	May 23, 25, 29. 2 cc each.	May 29	20	—
4.	,,	,,	May 31	22	—
5.	,,	,,	June 2	24	—
6.	,,	,,	June 4	26	—
7.	,,	,,	June 5	27	Liver
8.	,,	,,	,,	,,	—
9.	,,	,,	,,	,,	Liver
10.	,,	,,	,,	,,	—
11.	,,	,,	June 17	34	—
12.	,,	,,	June 19	41	—
13.	,,	,,	,,	,,	—
14.	,,	,,	,,	,,	—

Two out of fourteen chickens or 14% had metastatic formations.

Controls of Experiment I.

No.	Date of Transpl'n	Date of Death	Living Days	Metastasis
1.	May 10, '21.	May 31	22	—
2.	,,	,,	,,	—
3.	,,	June 1	23	—
4.	,,	,,	,,	—
5.	,,	,,	,,	—
6.	,,	June 2	24	—
7.	,,	June 7	29	—
8.	,,	June 10	32	—
9.	,,	June 13	35	—
10.	,,	June 17	36	—

Thus in this group there was no case of metastatic formation.

Experiment II.

No.	Date of Transpl'n	Date of Inject'n	Date of Death	Living Days	Site of Metastasis
1.	July 30.	Aug. 11, 2 cc. Aug. 14, 4 cc.	Aug. 14	16	—
2.	,,	,,	Aug. 15	17	—

3.	July 30	Aug. 14. 4 cc.	Aug. 15	17	—
4.	,,	,,	Aug. 16	18	—
5.	,,	,,	,,	,,	Liver
6.	,,	,,	,,	,,	—
7.	,,	,,	Aug, 19	21	—
8.	,,	,,	,,	,,	—
9.	,,	,,	Aug, 21	23	Liver
10.	,,	,,	Aug, 23	25	—
11.	,,	,,	Aug, 24	26	—

There were 2 chickens or 18% of metastatic formations out of 11 ckichens.

Controls of Experiment II.

No.	Date of Transpl'n	Date of Death	Living Days	Metastasis
1.	July 30. '21	Aug. 16	18	—
2.	,,	19	21	—
3.	,,	25	27	—
4.	,,	,,	,,	—
5.	,,	26	28	—
6.	,,	27	29	—
7.	,,	,,	,,	Liver
8.	,,	30	32	—
9.	,,	,,	,,	—
10.	,,	Sept. 1	34	—
11.	,,	,,	,,	—
12.	,,	,,	,,	—
13.	,,	2	35	—

There was 1 or 8% out of 13 chickens which had metastasis.

Experiment III.

No.	Date of Transpl'n	Date of Inject'n	Date of Death	Living Days	Metastasis
1.	Aug, 10. '21	Aug. 24, 27. 3 cc. each.	Aug. 29	20	—
2.	,,	Aug. 27, 30. 3 cc. each.	Aug. 30	21	—
3.	,,	,,	,,	,,	—
4.	,,	,,	Sept. 1	23	—
5.	,,	,,	,,	,,	—
6.	,,	,,	4	26	—

7.	Aug. 10, '21	„	Sept. 4	26	—
8.	„	„	5	27	—
9.	„	„	10	32	—

Thus there was no metastatic formation.

Controls of the Experiment III.

No.	Date of Transpl'n	Date of Death	Living Days	Metastasis
1.	Aug. 10. '21.	Sept. 3	25	—
2.	„	„	„	—
3.	„	4	26	—
4.	„	7	29	—
5.	„	12	34	—
6.	„	15	37	—
7.	„	19	41	—
8.	„	„	„	—

Thus there was no metastatic formation.

Experiment IV.

No.	Date of Transpl'n	Date of Injec'n	Date of Death	Living Days	Metastasis
1.	Dec. 16. '21.	Jan. 4, 7. 5 cc. each.	Jan. 4	19	—
2.	„	„	„	„	—
3.	„	„	7	22	—
4.	„	„	8	23	—
5.	„	„	„	„	—
6.	„	„	10	25	—
7.	„	„	„	„	—
8.	„	„	12	27	—
9.	„	„	13	28	—
10.	„	„	21	37	Liver
11.	„	„	„	„	Liver
12.	„	„	22	38	—
13.	„	„	„	„	—

There was 15% of metastatic formation, or 2 out of 13 chickens.

Controls of the Experiment IV.

No.	Date of Transpl'n	Date of Death	Living Days	Metastasis
1.	Dec. 18. '21.	Jan. 3	18	—
2.	"	4	19	—
3.	"	5	20	—
4.	"	12	27	—
5.	"	14	29	—
6.	"	15	30	—
7.	"	19	34	—
8.	"	22	38	—
9.	"	"	"	—
10.	"	23	39	Liver
11.	"	"	"	—
12.	"	24	40	—
13.	"	27	43	—

There was one case or 8% of metastatic formation out of 13 chickens.

The Results of Experiments.

In the experiment I, out of 14 chickens there were 2 chickens or 14% of metastatic formations, while the controls had none. In the experiment II, there were 2 chickens out of 11 chickens which had metastasis or 18%, while the controls had 8% of formations, or out of 13 chickens. The experiment IV showed out of 13 chickens which had metastasis or 15%, while the controls had 1 out of 13 which had metastasis or 8%. Thus in all these cases the number of metastatic formations are more in those cases which had been injected with phenylhydrazine than the control cases. Only in the experiment III showed no differences between the main experiment and the controls, both having no metastatic formations. In short when anemia is caused by injection of phenylhydrazine in chickens transplanted with sarcoma the percentage of metastatic formation is greater.

In concension a word of thanks is due to Professor Nagayo und Dr. Ogata for their constant advices, and also Professor Irisawa for his kindness. *(Author's abstract.)*

Studies on Metastasis-Formation of Mouse Carcinoma.

By

Shuzo Okonogi and **Kenji Tadenuma.**

One of us, Tadenuma, studied the influence of anemia, caused by injecting phenylhydrazine, on metastatic formation of chicken sorcoma. We carried out the same experiment with mouse carcinoma, the results of which are included in this report.

The strain of carcinoma used in this experiment was the same as that we used in the study of metastatic formation by bleeding. It was originally the strain No 63 of the London Royal Cancer Research Laboratory.

Method of Experiment.

A large number of English mouse, having the same conditions as much as possible, were selected for the experiment. After the injection of the emulsion of carcinomatous tissue under the skin of the back, those animals which had distinctly positive growths were used. They were divided into two groups. One group received injections of phenylhydrazine solution and the other was left untreated for controls. Those which died within a few hours after the injection of phenylhydrazine were not counted in the number. The experiment was extended from April to December 1921, in order to observe seasonal influnece.

Experiment I.

The animals were transplanted with the carcinoma on May 14, 1921. On the 28 th and 31 st of the same month, they were injected with 0.2 cc. of one thousand times diluted phenylhydrazine. Of thirty two animals seven had metastatis, or 22% of the total

number. They lived from 22 days to 40 days.

Three out of twenty seven animals had metastasis in the control group or 11%. They lived from 30 days to 41 days.

Experiment. II.

The animals were transplanted with carcinoma on May 5, 1921. On the 18 th, 20 th, 22 nd, 24 th, 26 th and 28 th, they received 0.1 cc. of one thousand times diluted solution. There were eight metastatic animals out of twenty four animals, or 33%. They lived from 22 days to 32 days.

Three out of sixteen control animals or 19% had metastasis. They lived from 24 days to 33 days.

Experiment III.

The animals were transplanted with carcinoma on June 18, 1921. On June 30 th, July 5 th and 13 th they were injected with 0.1 cc. of four hundred times diluted solution. Four out of thirteen animals or 30% had metastasis. While in the control group one out of eleven animals or 9.9% had metastasis.

Experiment IV.

The animals were transplanted with carcinoma on June 18, 1921. On July 2 nd, 5 th, 8 th and 11 th, they received 0.1 cc. of one thousand times diluted solution. There were two out of fifteen animals or 13.3% of metastatic formations. They lived from 24 days to 32 days. While one out of eight control animals or 12.5% had metastasis. It lived 31 days.

Experiment V.

The animals were transplanted with carcinoma on July 2, 1921. On July 13 th, 16 th and 19 th, they received 0.1 cc. of one thousand times diluted solution. There were four out of eighteen animals or 22% of metastatic formations. They lived

from 31 days to 36 days. In the control animals only one out of nine or 12% had metastasis. It lived 28 days.

Experiment VI.

The animals were transplanted with carcinoma on August 28, 1921. On September 2 nd, 7 th and 15 th, they received 0.1 cc. of four hundred times diluted solution. There were two metastatic formations out of twenty animals or 10%. One lived 28 days and the other lived 33 days. One out of sixteen control animals or 6% had metastasis. It lived 26 days.

Experiment VII.

The animals were transplanted with carcinoma on September 15, 1921. On September 28 th, 30 th and October 7 th, they received 0.1 cc. of four hundred times diluted solution. There were five out of twenty one animals or 24% of metastatic formations. They lived from 27 days to 38 days. While three out of fourteen control animals or 21% had metastasis. They lived from 21 days to 38 days.

Experiment VIII.

The animals were transplanted with carcinoma on September 24, 1921. On October 18 th, 25 th and 29 th, they received 0.1 cc. of one thousand times diluted solution. There were three out of eight animals or 37% of metastatic formations. They lived from 40 days to 56 days. While one out of six control animals or 16% had metastasis. It lived 37 days.

Thus without single exception, all the experiments show that metastases form more in the animals which received phenylhydrazine injection than the control animals. Out of the total number of one hundred forty three animals which received the injection of phenylhydrazine thirty five or 24% had metastases. While one hundred and seven control animals thirteen or 12.1% had metastases.

Viscera In which Metastases were Formed.

The metastases were formed the most in the liver in the experimental animals. The next in the order of frequency were lung, kidney and spleen. Out of thirty five animals which had metastases twenty five or 77% had metastases in livers. There were six metastatic formations in lungs and four in kidneys and two in spleens. While in the control animals twelve had metastases in liver out of thirteen animals which had metastases, and only one had it in lung.

Comparison with Bleeding Experiments.

In the bleeding experiments which we carried out two years ago there were 52% of metastatic formations. When this result is compared with that of present experiment which was 24% metastatic formations, the latter is quite distinctly less. In the control animals with bleeding experiments there were 9% of metastatic formations, while in the present experiment there were 13% of metastatic formations. Thus in bleeding there must be some other factors than anemia which influence metastatic formations.

Conclusions.

When anemia is produced in English mouse transplanted with carcinoma, by injecting phenylhydrazine solution, the rate of metastatic formation is higher. Thus with carcinoma, like chicken sarcoma, anemia is a factor for metastatic formation. The metastatic formation by bleeding is also due to anemia to a certain extent.

In conclusion, we wish to express our thanks to Prof. Nagayo and Assistant Prof Ogata for their valuable advices and to pay respects to Prof. Irisawa. *(Authors' abstract.)*

PLATE VI.

Fig. 1.

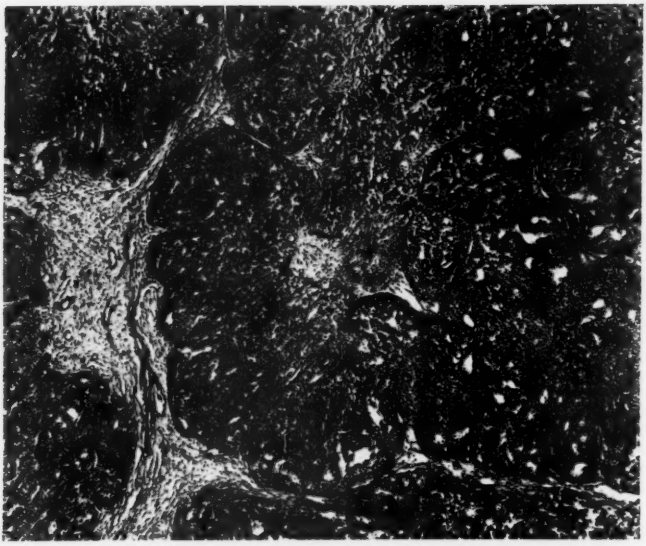
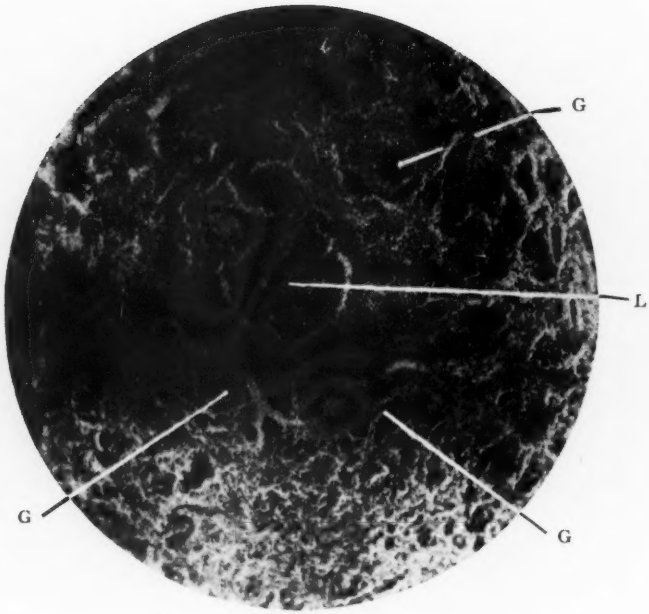


Fig. 2.

(T. Kimura and S. Taguma.)

PLATE V.



(I. Honda.)

PLATE IV.

Fig. 1.

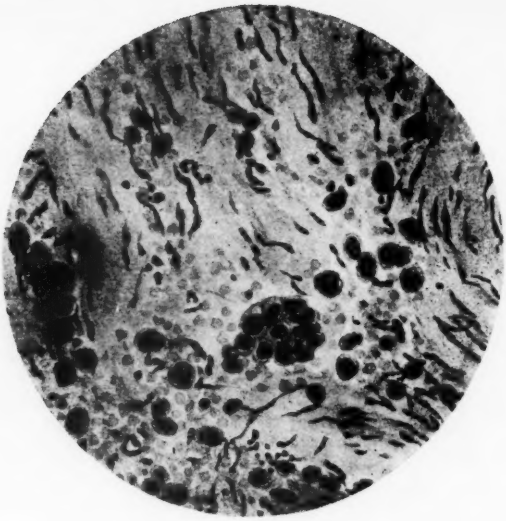


Fig. 2.

(Eguchi)

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